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Serial No. 10/535,268	: Group Art Unit 1624
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IMIDAZOLE DERIVATIVE, THEIR PRODUCTION AND USE

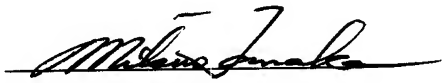
VERIFICATION OF ENGLISH TRANSLATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mitsuo TANAKA, declare that I am conversant in both the Japanese and English languages and that the English translation as attached hereto is an accurate translation of Japanese Patent Application No. 2002-338939 filed on November 22, 2002.

Signed this 30th day of January, 2009.



Mitsuo TANAKA

PATENT OFFICE

JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Application Number: Patent Application No. 2002-338939

Applicant(s): TAKEDA PHARMACEUTICAL COMPANY LIMITED
(TAKEDA CHEMICAL INDUSTRIES, LTD.)

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Document Name: Specification

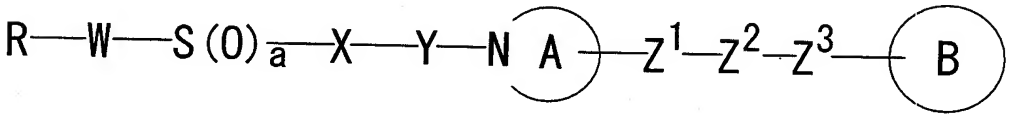
Title of the Invention:

IMIDAZOLE DERIVATIVES, THEIR PRODUCTION AND USE

Claims:

1. A compound represented by the formula (I):

[Chemical formula 1]



(I)

wherein R represents an optionally substituted cyclic hydrocarbon group or an optionally substituted heterocyclic group, W represents a bond or an optionally substituted divalent linear hydrocarbon group, X represents an optionally substituted divalent hydrocarbon group, Y represents -CO-, -S(O)-, $-S(O)_2-$ or a bond, ring A represents an optionally substituted pyrrolidine ring, an optionally substituted piperidine ring or an optionally substituted perhydroazepine ring, Z^1 and Z^3 independently represent a bond or an optionally substituted divalent linear hydrocarbon group, Z^2 represents $-N(R^1)-$, -O-, -S(O)-, $-S(O)_2-$, -CO-, $-CH(R^1)-$ or a bond (R^1 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, an optionally esterified carboxyl group or an optionally substituted carbamoyl group), ring B represents an optionally substituted imidazole ring, wherein a substituent which the

optionally substituted imidazole ring represented by ring B may have may be taken together with R^1 to form an optionally substituted ring, and a represents 0, 1 or 2, or a salt thereof.

2. A prodrug of the compound according to claim 1.

3. The compound according to claim 1, wherein R is an optionally substituted aryl group.

4. The compound according to claim 1, wherein R is naphthyl optionally substituted with a halogen atom or indolyl optionally substituted with a halogen atom.

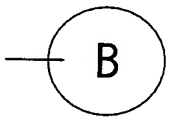
5. The compound according to claim 1, wherein W is a bond.

6. The compound according to claim 1, wherein X is an optionally substituted divalent linear hydrocarbon group.

7. The compound according to claim 1, wherein Y is -CO-.

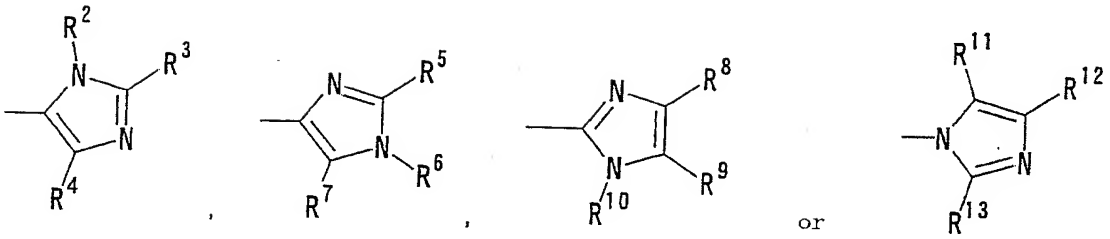
8. The compound according to claim 1, wherein ring A is an optionally substituted piperidine ring.

9. The compound according to claim 1, wherein the



is the formula:

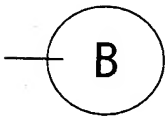
[Chemical formula 3]



wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^2 and R^3, R^5 and R^6, R^6 and R^7, R^8 and R^9, R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an optionally substituted ring.

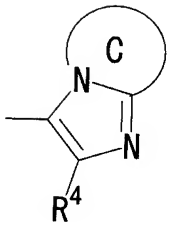
10. The compound according to claim 1, wherein the formula:

[Chemical formula 4]



is the formula:

[Chemical formula 5]



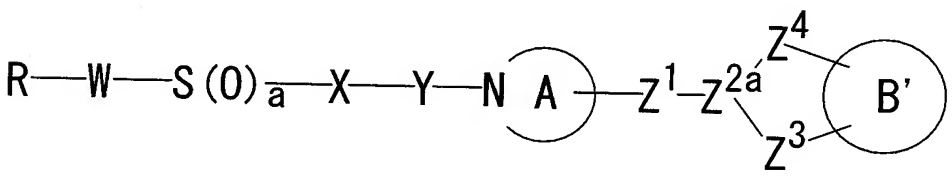
wherein ring C represents an optionally substituted nitrogen-containing heterocyclic ring, and other symbols are as defined above.

11. The compound according to claim 1, wherein a substituent which the optionally substituted imidazole ring represented by ring B may have and R^1 together do not form a ring.

12. The compound according to claim 1, wherein Z^2 is $-N(R^1)-$ or $-CH(R^1)-$ (R^1 is as defined above), and a substituent which the optionally substituted imidazole ring represented by ring B may have and R^1 are taken together to form an optionally substituted ring.

13. The compound according to claim 1, wherein the formula (I) is the formula (Ia):

[Chemical formula 6]



(Ia)

wherein ring B' represents an optionally further substituted imidazole ring, Z^{2a} represents N or CH, Z^4 represents an optionally substituted divalent linear

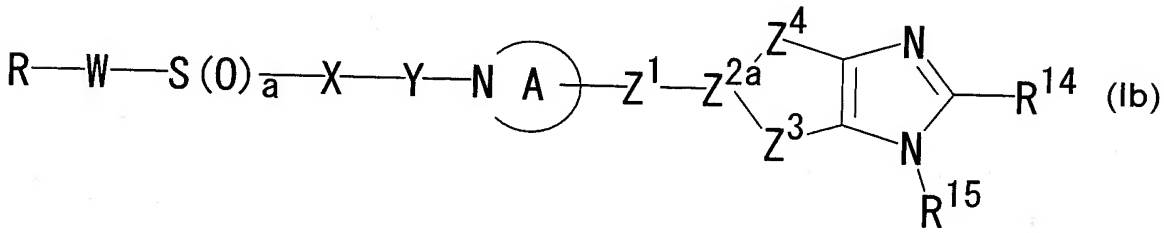
hydrocarbon group, and other symbols are as defined in claim 1.

14. The compound according to claim 13, wherein Z^{2a} is a nitrogen atom.

15. The compound according to claim 13, wherein Z^3 and Z^4 are independently a divalent linear hydrocarbon group optionally substituted with an oxo group.

16. The compound according to claim 1, wherein the formula (I) is the formula (Ib):

[Chemical formula 7]



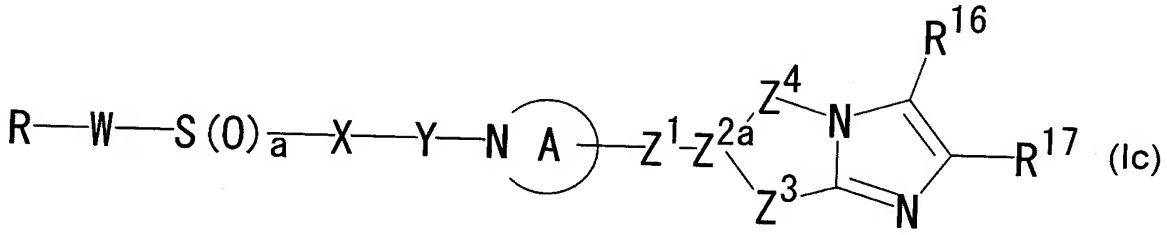
(Ib)

wherein R^{14} and R^{15} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group, or an optionally substituted amino group, or R^{14} and R^{15} may be taken together to form an optionally substituted ring, and other symbols are as defined above.

17. The compound according to claim 1, wherein the

formula (I) is the formula (Ic):

[Chemical formula 8]

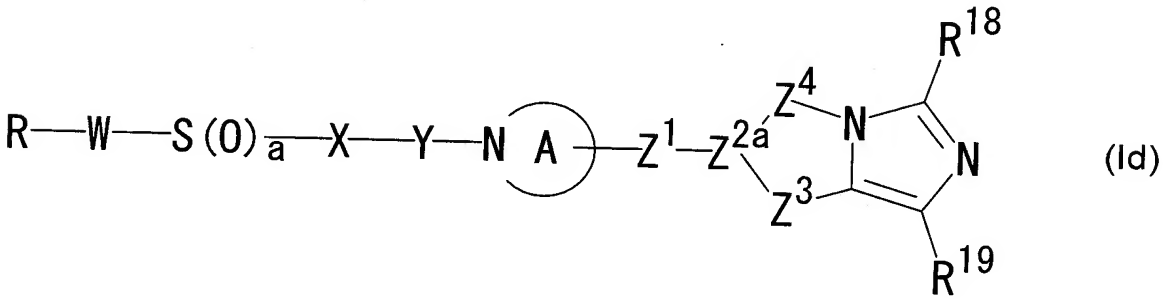


(Ic)

wherein R^{16} and R^{17} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^{16} and R^{17} may be taken together to form an optionally substituted ring, and other symbols are as defined above.

18. The compound according to claim 1, wherein the formula (I) is the formula (Id):

[Chemical formula 9]



(Id)

wherein R^{18} and R^{19} independently represent a hydrogen atom,

an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group, or an optionally substituted amino group, and other symbols are as defined above.

19. The compound according to claim 1, wherein a is 2.

20. A pharmaceutical preparation which comprises the compound according to claim 1 or 2.

21. The pharmaceutical preparation according to claim 20, which is an anticoagulant.

22. The pharmaceutical preparation according to claim 20, which is an activated blood coagulation factor X inhibitor.

23. The pharmaceutical preparation according to claim 20, which is an agent for preventing or treating myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism or thromboembolism during or after an operation.

Detailed Description of the Invention:

[0001]

Technical Field of the Invention

The present invention relates to a novel imidazole

derivative useful for preventing or treating arterial and venous thrombotic obstructive disease, inflammation, cancer and the like, which has anti-coagulation activity and anti-thrombosis activity by inhibiting activated blood coagulation factor X (FXa), and production and use thereof.

[0002]

Prior Art

For preventing and treating myocardial infarction, cerebral thrombosis and the like, it is important to inhibit formation of thrombi and, an anti-thrombin agent, a platelet aggregation inhibitor and the like as a thrombosis inhibitor have been studied and developed variously. However, as well as a platelet aggregation inhibitor, an anti-thrombin agent not only has anti-coagulation activity but also inhibits aggregation of platelet. Thus these drugs tend to cause bleeding or the like as side effect and thereby have a problem of their safety. On the other hand, it is thought that an FXa inhibitor inhibits only a coagulation factor specifically and therefore it may be a safe anticoagulant.

To date, compounds having FXa inhibiting activity have been disclosed, for example, in Patent Reference 1 to 6 and Non-patent Reference 1, etc.

[0003]

Patent Reference 1: JP-A 7-112970

Patent Reference 2: JP-A 5-208946

Patent Reference 3: WO 96/16940

Patent Reference 4: WO 96/40679

Patent Reference 5: WO 96/10022

Patent Reference 6: WO 02/06234

Non-patent Reference 1: Journal of Medicinal Chemistry, 1998, vol.41, p.3357

[0004]

Problem to be Solved by the Invention

There is a need for development of a novel compound useful as a thrombosis treating agent, which has improved drug efficacy, oral absorbability and duration of action and has fewer side effects, as compared with previous FXa inhibitors.

[0005]

Means for Solving the Problem

The present inventors studied intensively, considering that an imidazole derivative having high selectivity for and potent inhibitory activity on FXa may exert lasting and sufficient effect when orally administered and therefore it may be useful for preventing and treating arterial and venous thrombotic obstructive disease, inflammation and cancer.

As a result, the present inventors found that a novel imidazole derivative represented by the following formula

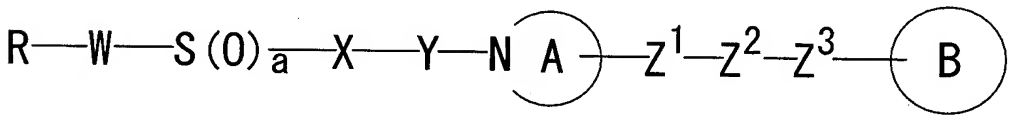
(I) or a salt thereof [hereinafter referred to as Compound (I) in some cases] has selective and potent FXa inhibitory activity, is highly safe, and exerts lasting and sufficient effect when orally administered, and then completed the present invention.

[0006]

That it, the present invention relates to:

(1) a compound represented by the formula (I):

[Chemical formula 10]



(I)

wherein R represents an optionally substituted cyclic hydrocarbon group or an optionally substituted heterocyclic group, W represents a bond or an optionally substituted divalent linear hydrocarbon group, X represents an optionally substituted divalent hydrocarbon group, Y represents -CO-, -S(O)-, $-S(O)_2-$ or a bond, ring A represents an optionally substituted pyrrolidine ring, an optionally substituted piperidine ring or an optionally substituted perhydroazepine ring, Z^1 and Z^3 independently represent a bond or an optionally substituted divalent linear hydrocarbon group, Z^2 represents $-N(R^1)-$, -O-, -S(O)-, $-S(O)_2-$, -CO-, $-CH(R^1)-$ or a bond (R^1 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, an optionally

esterified carboxyl group or an optionally substituted carbamoyl group), ring B represents an optionally substituted imidazole ring, wherein a substituent which the optionally substituted imidazole ring represented by ring B may have may be taken together with R^1 to form an optionally substituted ring, and a represents 0, 1 or 2, or a salt thereof;

(2) a prodrug of the compound according to the above (1);

(3) the compound according to the above (1), wherein R is an optionally substituted aryl group;

(4) the compound according to the above (1), wherein R is naphthyl optionally substituted with a halogen atom or indolyl optionally substituted with a halogen atom;

(5) the compound according to the above (1), wherein W is a bond;

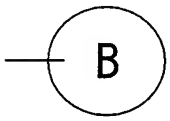
(6) the compound according to the above (1), wherein X is an optionally substituted divalent linear hydrocarbon group;

(7) the compound according to the above (1), wherein Y is -CO-;

(8) the compound according to the above (1), wherein ring A is an optionally substituted piperidine ring;

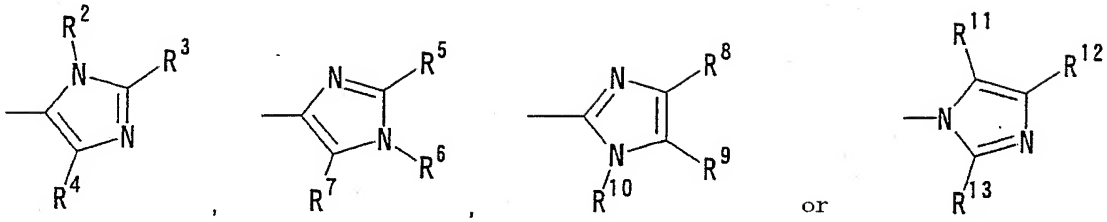
(9) the compound according to the above (1), wherein the formula:

[Chemical formula 11]



is the formula:

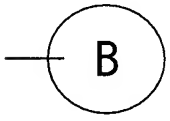
[Chemical formula 12]



wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^2 and R^3, R^5 and R^6, R^6 and R^7, R^8 and R^9, R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an optionally substituted ring;

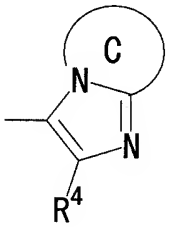
(10) the compound according to the above (1), wherein the formula:

[Chemical formula 13]



is the formula:

[Chemical formula 14]



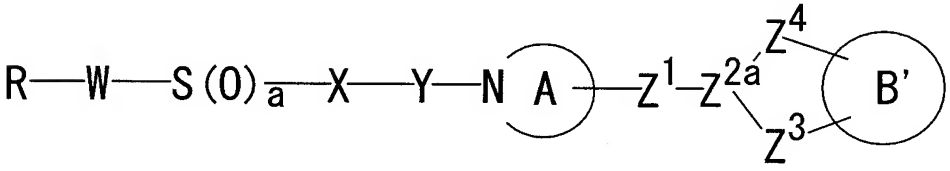
wherein ring C represents an optionally substituted nitrogen-containing heterocyclic ring, and other symbols are as defined above;

(11) the compound according to the above (1), wherein a substituent which the optionally substituted imidazole ring represented by ring B may have and R^1 do not form a ring;

(12) the compound according to the above (1), wherein Z^2 is $-N(R^1)-$ or $-CH(R^1)-$ (R^1 is as defined above), and a substituent which the optionally substituted imidazole ring represented by ring B may have and R^1 are taken together to form an optionally substituted ring;

(13) the compound according to the above (1), wherein the formula (I) is the formula (Ia):

[Chemical formula 15]



(Ia)

wherein ring B′ represents an optionally further

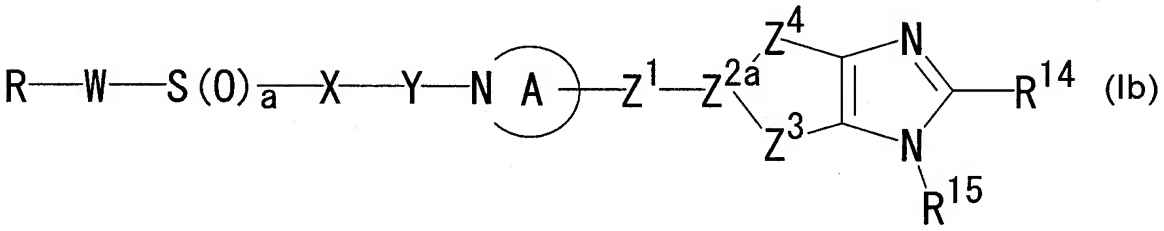
substituted imidazole ring, Z^{2a} represents N or CH, Z^4 represents an optionally substituted divalent linear hydrocarbon group, and other symbols are as defined in the above (1);

(14) the compound according to the above (13), wherein Z^{2a} is a nitrogen atom;

(15) the compound according to the above (13), wherein Z^3 and Z^4 are independently a divalent linear hydrocarbon group optionally substituted with an oxo group;

(16) the compound according to the above (1), wherein the formula (I) is the formula (Ib):

[Chemical formula 16]



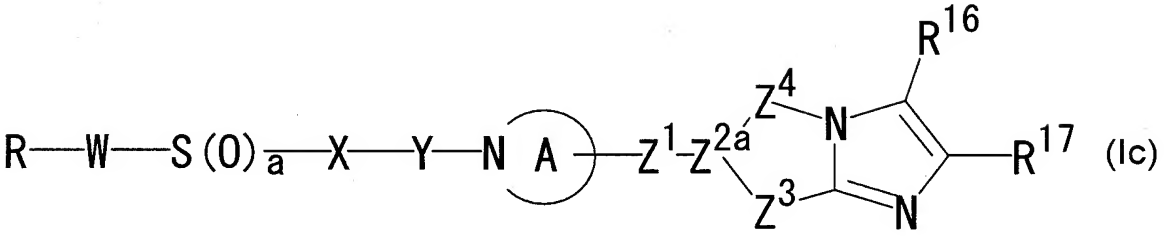
(Ib)

wherein R^{14} and R^{15} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group, or an optionally substituted amino group, or R^{14} and R^{15} may be taken together to form an optionally substituted ring, and

other symbols are as defined above;

(17) the compound according to the above (1), wherein the formula (I) is the formula (Ic):

[Chemical formula 17]

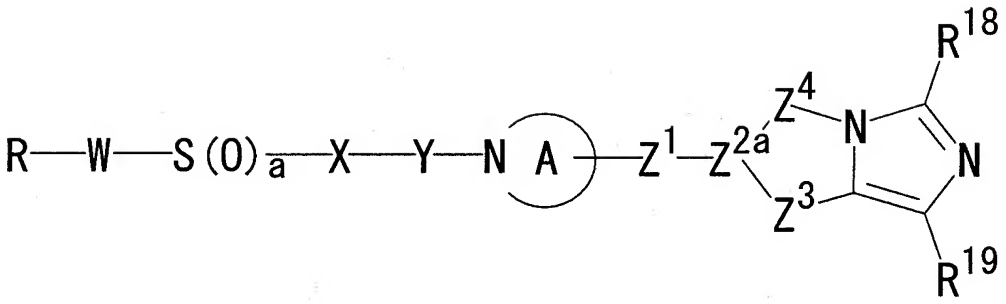


(Ic)

wherein R^{16} and R^{17} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^{16} and R^{17} may be taken together to form an optionally substituted ring, and other symbols are as defined above;

(18) the compound according to the above (1), wherein the formula (I) is the formula (Id):

[Chemical formula 18]



(Id)

wherein R^{18} and R^{19} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group, or an optionally substituted amino group, and other symbols are as defined above;

(19) the compound according to the above (1), wherein a is 2;

(20) a pharmaceutical preparation which comprises the compound according to the above (1) or (2);

(21) the pharmaceutical preparation according to the above (20), which is an anticoagulant;

(22) the pharmaceutical preparation according to the above (20), which is an activated blood coagulation factor X inhibitor;

(23) the pharmaceutical preparation according to the above (20), which is an agent for preventing or treating

myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism or thromboembolism during or after an operation; and the like.

[0007]

In the above formulas, R represents an optionally substituted cyclic hydrocarbon group, or an optionally substituted heterocyclic group (preferably optionally substituted aryl, or optionally substituted aromatic heterocyclic group).

The "cyclic hydrocarbon group" of the "optionally substituted cyclic hydrocarbon group" represented by R includes an alicyclic hydrocarbon group, an aryl group and the like and, among them, an aryl group is preferable.

The "alicyclic hydrocarbon group" as an example of a cyclic hydrocarbon group includes a saturated or unsaturated alicyclic hydrocarbon group such as a cycloalkyl group, a cycloalkenyl group, a cycloalkadienyl group, and the like.

Herein, the "cycloalkyl group" includes C_{3-9} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and the like.

The "cycloalkenyl group" includes a C_{3-9} cycloalkenyl group such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, 1-cyclohexen-1-yl, 1-cyclohepten-1-yl and

the like.

The "cycloalkadienyl group" includes a C_{4-6} cycloalkadienyl group such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like.

The "aryl group" as an example of a cyclic hydrocarbon group includes a monocyclic or fused polycyclic aromatic hydrocarbon group. For example, a C_{6-14} aryl group such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and the like and, among them, phenyl, 1-naphthyl, 2-naphthyl and the like are particularly preferable.

In addition, a cyclic hydrocarbon group includes a dicyclic or tricyclic hydrocarbon group derived from fusion of same or different two to three rings (preferably two or more kinds of rings) selected from rings constituting the aforementioned alicyclic hydrocarbon group and aromatic hydrocarbon group, such as 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, indenyl, dihydrobenzocycloheptenyl and fluorenyl.

[0008]

The "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R includes an aromatic heterocyclic group, a saturated or unsaturated non-aromatic heterocyclic group (aliphatic heterocyclic group) containing at least one (preferably one to four, more preferably one to two) 1 to 3 (preferably 1 to 2)

kinds of heteroatoms selected from an oxygen atom, a sulfur atom, and a nitrogen atom as a ring system-constituting atom (ring atom) and the like.

The "aromatic heterocyclic group" includes a 5 to 6-membered aromatic monocyclic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like, and a 8 to 16-membered (preferably 8 to 12-membered) aromatic fused heterocyclic group such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-

triazolo[4,3-b]pyridazinyl and the like, preferably, a heterocyclic ring in which 1 to 2 (preferably 1) of the aforementioned 5 to 6-membered aromatic monocyclic heterocyclic groups are fused with 1 to 2 (preferably 1) of benzene rings, or a heterocyclic ring in which 2 to 3 (preferably 2) of the same or different aforementioned 5 to 6-membered aromatic monocyclic heterocyclic groups are fused, more preferably a heterocyclic ring in which the aforementioned 5 to 6-membered aromatic monocyclic heterocyclic group is fused with a benzene ring, particularly preferably indolyl, benzofuranyl, benzo[b]thienyl, benzopyranyl.

The "non-aromatic heterocyclic group" includes a 3 to 8-membered (preferably 5 to 6-membered) saturated or unsaturated (preferably saturated) non-aromatic monocyclic heterocyclic group (aliphatic monocyclic heterocyclic group) such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like, a heterocyclic group in which 1 to 2 (preferably 1) of the aforementioned non-aromatic monocyclic heterocyclic groups are fused with 1 to 2 (preferably 1) of benzene rings such as 1,3-dihydroisoindolyl and the like, a heterocyclic group in which 1 to 2 (preferably 1) of the aforementioned non-

aromatic monocyclic heterocyclic groups are fused with 1 to 2 (preferably 1) of 5 to 6-membered aromatic monocyclic heterocyclic groups, and a non-aromatic heterocyclic group in which a part or all of the double bonds of the aforementioned aromatic monocyclic heterocyclic group or aromatic fused heterocyclic group is saturated, such as 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl.

[0009]

Examples of a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R include optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclic group, optionally substituted amino, optionally substituted imidoyl (e.g. a group represented by the formula -C(U')=N-U, wherein U and U' represent a hydrogen atom or a substituent respectively (U represents preferably a hydrogen atom) etc.), optionally substituted amidino (e.g. a group represented by the formula -C(NT'T'')=N-T, wherein T, T' and T'' represent a hydrogen atom or a substituent respectively (T represents preferably a hydrogen atom) etc.), an optionally substituted hydroxy group, an optionally substituted thiol group, optionally

substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally esterified carboxyl, optionally substituted carbamoyl, optionally substituted thiocarbamoyl, an optionally substituted sulfamoyl group, a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc. preferably chlorine, bromine etc.), a cyano group, a nitro group, a sulfonic acid-derived acyl, carboxylic acid-derived acyl and the like. These optional substituents may be at 1 to 5 (preferably 1 to 3) substitutable positions. In addition, the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R may have an oxo group or a thioxo group. For example, when R is benzopyranyl, R may form benzo-α-pyronyl or benzo-γ-pyronyl.

[0010]

The "aryl" of the "optionally substituted aryl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and the like. Herein, substituents for the aryl include a lower alkoxy group (e.g. C_{1-6} alkoxy such as methoxy, ethoxy, propoxy etc.), a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl etc.), lower

alkenyl (e.g. C_{2-6} alkenyl such as vinyl, allyl etc.), lower alkynyl (e.g. C_{2-6} alkynyl such as ethynyl, propargyl etc.), optionally substituted amino, an optionally substituted hydroxyl group, a cyano group, optionally substituted amidino, carboxy, a lower alkoxycarbonyl group (e.g. C_{1-6} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl etc.), an optionally substituted carbamoyl group (e.g. a carbamoyl group which may be substituted with C_{1-6} alkyl optionally substituted with 5 to 6-membered aromatic monocyclic heterocyclic group (e.g. pyridinyl etc.), acyl (e.g. formyl, C_{2-6} alkanoyl, benzoyl, optionally halogenated C_{1-6} alkylsulfonyl, benzenesulfonyl etc.) or optionally halogenated C_{1-6} alkoxycarbonyl), 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl (the sulfur atom may be oxidized), 1-piperazinylcarbonyl etc.). These optional substituents may be at 1 to 3 substitutable positions.

[0011]

The "optionally substituted amino", "optionally substituted hydroxyl group" and "optionally substituted amidino" exemplified as a substituent for the "optionally substituted aryl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by

R include the same groups as the "optionally substituted amino", "optionally substituted hydroxyl group" and "optionally substituted amidino" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R described later.

[0012]

The "alkyl" of the "optionally substituted alkyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes C_{1-6} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and the like. Herein, substituents for the alkyl include the same number of the same groups as those of a substituent for the aforementioned "optionally substituted aryl" and an oxo group, a thioxo group and the like.

The "alkenyl" of the "optionally substituted alkenyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, 2-methylallyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-

butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and the like. Herein, substituents for the alkenyl include the same number of the same groups as those of a substituent in the aforementioned "optionally substituted aryl", and an oxo group, a thioxo group and the like.

The "alkynyl" of the "optionally substituted alkynyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes C_{2-6} alkynyl such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. Herein, substituents for the alkynyl include the same number of the same substituents as those of a substituent for the aforementioned "optionally substituted aryl", and an oxo group, a thioxo group and the like.

[0013]

The "cycloalkyl" of the "optionally substituted cycloalkyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by

R includes C_{3-7} cycloclkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Herein, substituents for cycloalkyl include the same number of the same groups as those of a substituent for the aforementioned "optionally substituted aryl".

The "cycloalkenyl" of the "optionally substituted cycloalkenyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted hetercyclic group" represented by R includes C_{3-6} cycloalkenyl such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and the like. Herein, substituents for the cycloalkenyl include the same number of the same groups as those of a substituent for the aforementioned "optionally substituted aryl", and an oxo group, a thioxo group and the like.

[0014]

The "heterocyclic group" of the "optionally substituted heterocyclic group" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R is the same as the heterocyclic group of the "optionally substituted heterocyclic group" represented by R.

Substituents for the "optionally substituted heterocyclic group" include the same number of the same

groups as those of a substituent for the aforementioned "optionally substituted aryl", and an oxo group, a thioxo group and the like.

[0015]

Substituents for the "optionally substituted amino", the "optionally substituted imidoyl", the "optionally substituted amidino", the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl" and the "optionally substituted alkylsulfonyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R include, for example, lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl etc.) which may be substituted with a substituent selected from a halogen atom (e.g fluorine, chlorine, bromine, iodine etc.) and optionally halogenated C_{1-6} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, trichloromethoxy, 2,2,2-tricholoroethoxy etc.), acyl (C_{1-6} alkanoyl (e.g. formyl, acetyl, propionyl, valeroyl, pivaloyl etc.), benzoyl, C_{1-6} alkylsulfonyl (e.g. methanesulfonyl etc.), benzenesulfonyl etc.), optionally halogenated C_{1-6} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, trifluoromethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, tricholoromethoxycarbonyl, 2,2,2-

trichloroethoxycarbonyl etc.), C_{1-6} alkoxycarbonyl optionally substituted with phenyl (e.g. benzyloxycarbonyl etc.), a hetrocyclic group (the same group as the "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R) and the like. The "amino" of the "optionally substituted amino" as a substituent may be substituted with optionally substituted imidoyl (e.g. C_{1-6} alkylimidoyl (e.g. formylimidoyl, acetylimidoyl etc.), C_{1-6} alkoxyimidoyl, C_{1-6} alkylthioimidoyl, amidino etc.), amino which may be substituted with 1 to 2 C_{1-6} alkyl groups, or the like, or two substituents may be taken together with a nitrogen atom to form cyclic amino. Such cyclic amino includes 3 to 8-membered (preferably 5 to 6-membered) cyclic amino such as 1-azetidinyl, 1-pyrrolidinyl, piperidino, thiomorpholino, morpholino, 1-piperazinyl, 1-piperazinyl which may have lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl and the like), aralkyl (e.g. C_{7-10} aralkyl such as benzyl, phenethyl etc.), aryl (e.g. C_{6-10} aryl such as phenyl, 1-naphthyl, 2-naphthyl etc.) or the like at the 4-position, 1-pyrrolyl, 1-imidazolyl and the like.

[0016]

The "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted cyclic

hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes, in addition to free carboxyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and the like.

The "lower alkoxycarbonyl" includes C_{1-6} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl and the like. Among them, C_{1-3} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like is preferable.

As the "aryloxycarbonyl", C_{7-12} aryloxycarbonyl such as phenoxycarbonyl, 1-naphthoxycarbonyl, 2-naphthoxycarbonyl and the like is preferable.

As the "aralkyloxycarbonyl", C_{7-10} aralkyloxycarbonyl such as benzyloxycarbonyl, phenethyloxycarbonyl and the like (preferably, C_{6-10} aryl-C_{1-4} alkoxy-carbonyl etc.) is preferable.

The "aryloxycarbonyl" and the "aralkyloxycarbonyl" may have a substituent and, such a substituent and the number thereof used are the same as a substituent for aryl or aralkyl exemplified as a substituent for N-mono-substituted carbamoyl described above.

[0017]

The "optionally substituted carbamoyl" exemplified as

a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes, in addition to non-substituted carbamoyl, N-mono-substituted carbamoyl and N,N-di-substituted carbamoyl.

A substituent for the "N-mono-substituted carbamoyl" includes lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl etc.), lower alkenyl (e.g. C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, propenyl, butenyl, pentenyl, hexenyl etc.), cycloalkyl (e.g. C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc.), aryl (e.g. C_{6-10} aryl such as phenyl, 1-naphtyl, 2-naphthyl etc.), aralkyl (e.g. C_{7-10} aralkyl such as benzyl, phenethyl etc., preferably phenyl-C_{1-4} alkyl etc.), arylalkenyl (e.g. C_{8-10} alylalkenyl such as cinnamyl etc., preferably phenyl-C_{2-4} alkenyl etc.), a heterocyclic group (e.g. the same group as the "heterocyclic group" of the "optionally substituted heterocyclic group" represented by R), amino optionally substituted with 1 to 2 C_{1-6} alkyl groups and the like. The lower alkyl, the lower alkenyl, the cycloalkyl, the aryl, the aralkyl, the arylalkenyl and the heterocyclic group may have a substituent. Such a substituent includes a hydroxyl group, optionally substituted amino [the amino may be substituted with 1 or 2 substituents such as lower alkyl

(e.g. C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl etc.), acyl (e.g. C_{1-6} alkanoyl such as formyl, acetyl, propionyl, pivaloyl etc., benzoyl etc.), carboxyl, C_{1-6}-alkoxycarbonyl etc.], a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), a nitro group, a cyano group, lower alkyl optionally substituted with 1 to 5 halogen atoms (e.g. fluorine, chlorine, bromine, iodine etc.), lower alkoxy optionally substituted with 1 to 5 halogen atoms (e.g. fluorine, chlorine, bromine, iodine etc.) and the like. The lower alkyl includes C_{1-6} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like. Particularly, methyl, ethyl and the like are preferable. The lower alkoxy includes C_{1-6} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like. In particular, methoxy, ethoxy and the like are preferable. In addition, it is preferable that 1 or 2 or 3 (preferably 1 or 2) of these substituents, which may be the same or different each other, are used.

The "N,N-di-substituted carbamoyl" means a carbamoyl group having two substituents on the nitrogen atom. One of the substituents includes the same substituents as the aforementioned substituents for the "N-mono-substituted carbamoyl", and the other includes lower alkyl (e.g. C_{1-6}

alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl etc.), C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc.), C_{7-10} aralkyl (e.g. benzyl, phenethyl etc., preferably phenyl-C_{1-4} alkyl etc.) and the like. The two substituents may be taken together with the nitrogen atom to form a cyclic amino. Such cyclic aminocarbamoyl includes 3- to 8-membered (preferably 5 to 6-membered) cyclic amimocarbonyl such as 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl (the sulfur atom may be oxidized), 1-piperazinylcarbonyl, 1-piperazinylcarbonyl optionally having lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl etc.), aralkyl (e.g. C_{7-10} aralkyl such as benzyl, phenethyl etc.), aryl (e.g. C_{6-10} aryl such as phenyl, 1-naphthyl, 2-naphthyl etc.) and the like at the 4-position, and the like.

Substituents for the "optionally substituted thiocarbamoyl" and the "optionally substituted sulfamoyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R are the same as substituents for the aforementioned "optionally substituted carbamoyl".

[0018]

The "sulfonic acid-derived acid" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes a group obtained by binding of one substituent on the nitrogen atom of the aforementioned "N-mono-substituted carbamoyl" and sulfonyl, and preferable examples include acyl such as C_{1-6} alkylsulfonyl such as methanesulfonyl and ethanesulfonyl, benzenesulfonyl and p-toluenesulfonyl.

The "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" and the "optionally substituted heterocyclic group" represented by R includes a group obtained by binding of a hydrogen atom or one substituent on the nitrogen atom of the aforementioned "N-mono-substituted carbamoyl" and carbonyl, and preferable examples include acyl such as C_{1-6} alkanoyl such as formyl, acetyl, propionyl and pivaloyl, and benzoyl.

[0019]

R may be preferably an aryl group which may be substituted with a substituent selected from a halogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, optionally substituted amino, nitro, cyano, optionally substituted amidino and optionally esterified or amidated carbonyl; or a heterocyclic group which may be substituted with a

substituent selected from a halogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, optionally substituted amino, nitro, cyano, optionally substituted amidino and optionally esterified or amidated carboxyl.

Among them, preferably R may be optionally substituted aryl, especially, aryl (preferably, C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl etc.) which may be substituted with a halogen atom or C_{2-4} alkenyl (preferably, a halogen atom).

In addition, preferably R may be an optionally substituted heterocyclic group, especially, a heterocyclic group (preferably, indolyl, benzofuranyl, benzopyranyl etc., more preferably indolyl) which may be substituted with a halogen atom.

Among them, R is preferably naphthyl optionally substituted with a halogen atom.

[0020]

In the above formulas, W represents a bond or an optionally substituted divalent linear hydrocarbon group.

The "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by W includes C_{1-6} alkylene (e.g. methylene, ethylene, trimethylene, tetramethylene etc.), C_{2-6} alkenylene (e.g. vinylene, propylene, 1-or 2-butenylene, butadienylene etc.) and C_{2-8} alkynylene (e.g. ethynylene, 1-

or 2-propynylene, 1- or 2- butynylene etc.).

Substituents for the "optionally substituted divalent linear hydrocarbon group" represented by W are the same as substituents for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R.

As W, for example, a bond or C_{1-6} alkenylene is preferable and, among them, a bond is more preferable.

[0021]

In the above formulas, X represents an optionally substituted divalent hydrocarbon group.

The "divalent hydrocarbon group" of the "optionally substituted divalent hydrocarbon group" represented by X includes a "divalent linear hydrocarbon group", a "divalent cyclic hydrocarbon group" and a combination thereof.

The "divalent linear hydrocarbon group" is, for example, the same as the "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by W as described above.

The "divalent cyclic hydrocarbon group" includes a "divalent cyclic hydrocarbon group" formed by removing any one hydrogen atom form the "cyclic hydrocarbon group" of the "optionally substituted cyclic hydrocarbon group" represented by R, and among them, a divalent aryl group, particularly a phenylene group is preferable, and such a phenylene group includes 1,2-phenylene, 1,3-phenylene and

1,4-phenylene.

As the "optionally substituted divalent hydrocarbon group" represented by X, an optionally substituted divalent linear hydrocarbon group and an optionally substituted phenylene group are preferable and, among them, optionally substituted C_{1-6} alkylene is preferable.

Substitutents for the "optionally substituted divalent hydrocarbon group" represented by X are the same as those for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R. Among them, preferred are lower alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, propyl etc.), lower alkenyl (e.g. C_{2-6} alkenyl such as vinyl, allyl etc.), lower alkynyl (e.g. C_{2-6} alkynyl such as ethynyl, propargyl etc.), optionally substituted amino, an optionally substituted hydroxyl group, a cyano group, optionally substituted amidino, carboxy, lower alkoxycarbonyl (e.g. C_{1-6} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl etc.), an optionally substituted carbamoyl group (e.g. a carbamoyl group optionally substituted with C_{1-6} alkyl or acyl (e.g. formyl, C_{2-6} alkanoyl, benzoyl, optionally halogenated C_{1-6} alkoxycarbonyl, optionally halogenated C_{1-6} alkylsulfonyl, benzenesulfonyl, p-toluenesulfonyl etc.) etc.) and an oxo group. These substituents may be at 1 to 3 optional substitutable positions.

As X, C_{1-6} alkylene is preferable. Among them, ethylene is particularly preferable.

[0022]

In the above formulas, Y represents -CO-, -S(O)-, -$S(O)_2$- or a bond.

As Y, -CO- is preferable.

[0023]

In the above formulas, ring A represents an optionally substituted pyrrolidine ring, an optionally substituted piperidine ring or an optionally substituted perhydroazepine ring.

Substituents for the "optionally substituted pyrrolidine ring", the "optionally substituted piperidine ring" and the "optionally substituted perhydroazepine ring" represented by ring A are the same group as those for the aforementioned "optionally substituted heterocyclic group" represented by R. These substituents may be at 1 to 5 (preferable 1 to 3) optional substitutable positions. Among them, a C_{1-6} alkyl group (optionally substituted with a C_{1-6} alkylsulfinyl group, a C_{1-6} alkylsulfonyl group, a hydroxyl group or an optionally esterified or amidated carboxyl), a hydroxyl group, an optionally esterified or amidated carboxyl group and an oxo group are preferable.

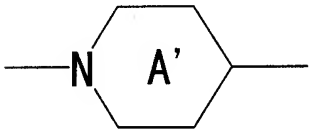
As ring A, an optionally substituted piperidine ring is preferable, among them, it is preferable that the

formula:

[Chemical formula 19]

is

[Chemical formula 20]



wherein ring A' may be substituted.

[0024]

In the above formulas, Z^1 and Z^3 independently represent a bond or an optionally substituted divalent linear hydrocarbon group.

The "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by Z^1 and Z^3, respectively, is the same as the "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by W.

Substituents for the "optionally substituted divalent linear hydrocarbon group" represented by Z^1 and Z^3, respectively, include the same groups and number as those of substituents for the "optionally substituted divalent linear hydrocarbon group" represented by W.

As Z^1, a bond and C_{1-6} alkylene are preferable.

As Z^3, a bond and C_{1-6} alkylene are preferable.

[0025]

In the above formulas, Z^2 represents $-N(R^1)-$, $-O-$, $-S(O)-$, $S(O)_2-$, $-CO-$, $-CH(R^1)-$ or a bond, wherein R^1 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, an optionally esterified carboxyl group or an optionally substituted carbamoyl group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^1 includes alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl and aralkyl.

The alkyl, the alkenyl, the alkynyl, the aryl, the cycloalkyl and the cycloalkenyl are the same as alkyl, alkenyl, alkynyl, aryl, cycloalkyl and cycloalkenyl of the "optionally substituted alkyl", the "optionally substituted alkenyl", the "optionally substituted alkynyl", the "optionally substituted aryl", the "optionally substituted cycloalkyl" and the "optionally substituted cycloalkenyl" exemplified as substituents for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R, respectively.

The aralkyl includes a C_{7-16} aralkyl group such as a phenyl-C_{1-6} alkyl group such as benzyl, phenethyl, 3-

phenylpropyl and 4-phenylbutyl, and naphthyl-C_{1-6} alkyl group such as (1-naphthyl)methyl, 2-(1-naphthyl)ethyl and 2-(2-naphthyl)ethyl.

Substituents for the "optionally substituted hydrocarbon group" represented by R^1 include the same groups and the same number as those of substituents for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted acyl group" represented by R^1 includes the same groups as the "sulfonic acid-derived acyl" and the "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally esterified carboxyl group" represented by R^1 includes the same group as the "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted carbamoyl group" represented by R^1 includes the same group as the "optionally substituted carbamoyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

As Z^2, $-N(R^1)-$, -CO- or a bond is preferable.

[0026]

Ring B represents an optionally substituted imidazole

ring.

Substituents for the optionally substituted imidazole ring are the same as those for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R (provided that an oxo group and a thioxo group are excluded). These optional substituents may be at 1 to 3 (preferably 1 to 2) substitutable positions.

[0027]

When an imidazole ring represented by ring B has a substituent, the substituent and R^1 may be taken together to form an "optionally substituted ring". The "ring" of the "optionally substituted ring" may be homocyclic or heterocyclic.

The "homocyclic or heterocyclic" ring includes (i) an aromatic or non-aromatic heterocyclic ring containing, preferably one to three, 1 or 2 kinds of heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, and (ii) cyclic hydrocarbon consisting of carbon atoms (homocyclic ring).

The "aromatic heterocyclic ring" includes a 5 to 6-membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (e.g. pyridine, pyrazine, pyrimidine, pyridazine, pyrrole, imidazole, pyrazole, triazole, thiophen, furan, thiazole,

isothiazole, oxazole and isoxazole rings).

The "non-aromatic heterocyclic ring" includes a 5 to 9-membered (preferably 5 or 6-membered) non-aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (e.g. tetrahydropyridine, dihydropyridine, tetrahydropyrazine, tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, dihydropyrrole, dihydrothiophen, dihydrofuran, piperidine, piperazine, hexahydropyrimidine, hexahydropyridazine, tetrahydropyran, morpholine, pyrrolidine, pyrazoline, imidazolidine, thiazoline, isothiazoline, oxazoline, isoxazoline, pyrazolidine, tetrahydrothiophen, tetrahydrofuran, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole ring etc).

The "cyclic hydrocarbon (homocyclic ring)" includes a 3 to 10-membered (preferably 5 to 9-membered, more preferably 5 or 6-membered) cyclic hydrocarbon, for example, benzene, C_{3-10} cycloalkene (e.g. cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene etc.), C_{3-10} cycloalkane (e.g.cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane etc.) and the like. Cycloalkene may be preferably C_{5-6} cycloalkene (e.g. cyclopentene, cyclohexne etc.) and cycloalkane may be preferably C_{5-6} cycloalkane (e.g. cyclohexane, cyclopentane).

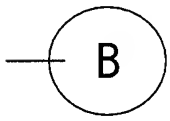
As a "ring" formed by binding of a substituent on an imidazole ring represented by ring B and R^1, for example, a 5 to 9-membered (preferably 5 or 6-membered) non-aromatic heterocyclic ring containing 1 to 2 (preferably 2) nitrogen atoms in addition to carbon atoms is preferable. Among them, more preferable examples thereof include tetrahydropyridine, tetrahydropyrazine, tetrahydropyrrole and tetrahydroimidazole.

Substituents for the "optionally substituted ring" formed by binding of a substituent on an imidazole ring represented by ring B and R^1 include the same group as substituents for the aforementioned "optionally substituted heterocyclic group" represented by R. These optional substituents may be at 1 to 3 (preferably 1 to 2) substitutable positions. As substituents for the "optionally substituted ring", among them, a C_{1-6} alkyl group optionally substituted with a hydroxyl group, a hydroxyl group, an oxo group and the like are preferable.

[0028]

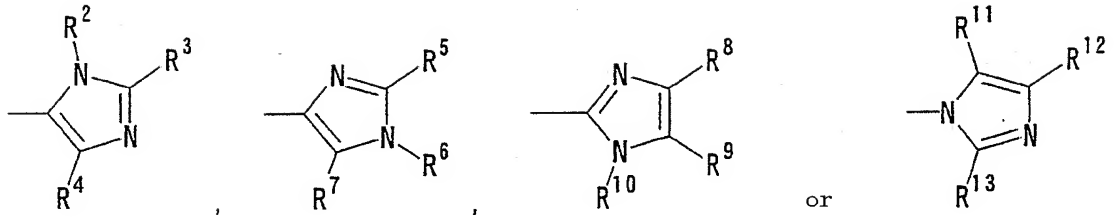
In ring B, the formula:

[Chemical formula 21]



is preferably

[Chemical formula 22]



wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^2 and R^3, R^5 and R^6, R^6 and R^7, R^8 and R^9, R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an optionally substituted ring.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} is, for example, the same as the "hydrocarbon group" of the aforementioned "optionally substituted hydrocarbon group" represented by R^1. Substituents for the "optionally substituted hydrocarbon group" include the same groups and number as those of a substituent for the aforementioned "optionally substituted hydrocarbon group" represented by R^1.

Substituents for the "optionally substituted hydroxyl

group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl group" and the "optionally substituted alkylsulfonyl group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} include the same groups as substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl" and the "optionally substituted alkylsulfonyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R, respectively.

The "optionally substituted acyl group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} includes the same groups as the "sulfonic acid-derived acyl" and the "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally esterified carboxyl group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} includes the same group as the "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted hydrocarbon group" represented R.

The "optionally substituted carbamoyl group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} includes the same group as the "optionally substituted carbamoyl" exemplified as a substituent for the

aforementioned "optionally substituted cyclic hydrocarbon group" represented by R^1.

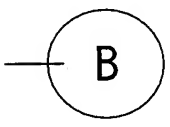
The "optionally substituted amino group" represented by R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} includes the same group as the "optionally substituted amino" exemplified as a substituent for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R.

The "ring" of the "optionally substituted ring" which may be formed by binding of R^2 and R^3, R^5 and R^6, R^6 and R^7, R^8 and R^9, R^9 and R^{10}, or R^{11} and R^{12} includes the same ring as the aforementioned "ring" formed by binding of a substituent on ring B and R^1. Substituents for the "optionally substituted ring" include the same group as substituents for the aforementioned "optionally substituted heterocyclic group" represented by R. These optional substituents may be at 1 to 5 (preferably 1 to 3) substitutable positions.

[0029]

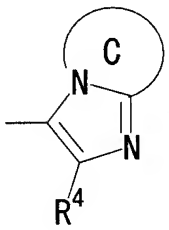
In a preferable aspect of ring B, for example, the formula:

[Chemical formula 23]



is

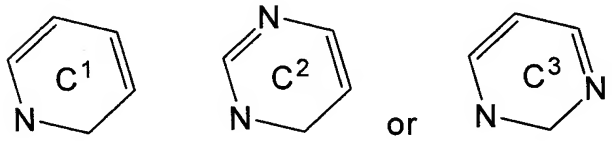
[Chemical formula 24]



wherein ring C represents an optionally substituted nitrogen-containing heterocyclic ring, and other symbols are same as defined above.

The "nitrogen-containing heterocyclic ring" of the "optionally substituted nitrogen-containing heterocyclic ring" represented by ring C includes a non-aromatic nitrogen-containing heterocyclic ring (e.g. pyrrolidine, piperidine, perhydroazepine etc.) or a ring which may be fused with an imidazole ring to form an aromatic fused nitrogen-containing heterocyclic ring (e.g. a ring represented by the formula:

[Chemical formula 25]



wherein rings C^1, C^2 and C^3 may be substituted, etc.).

Substituents for the "optionally substituted nitrogen-containing heterocyclic ring" represented by ring C (and substituents for rings C^1, C^2 and C^3) include the same groups as substituents for the aforementioned "optionally

substituted heterocyclic group" represented by R, and these optional substituents may be at 1 to 5 (preferably 1 to 3) substitutable positions.

[0030]

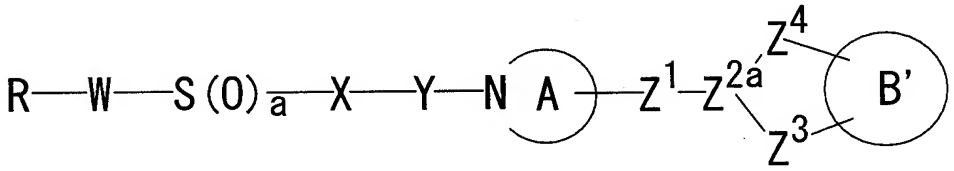
In a preferable aspect of a compound represented by the formula (I), for example, a substituent of an imidazole ring represented by ring B and R^1 together do not form a ring.

[0031]

In another preferable aspect of a compound represented by the formula (I), for example, Z^2 is $-N(R^1)-$ or $-CH(R^1)-$ (R^1 is as defined above) and a substituent of an imidazole ring represented by ring B is taken together with R^1 to form an optionally substituted ring.

In a preferable aspect of a compound represented by the formula (I), inter alia, the formula (I) is the formula (Ia):

[Chemical formula 26]



(Ia)

wherein ring B' represents an optionally further substituted imidazole ring, Z^{2a} represents N or CH, Z^4 represents an optionally substituted divalent linear hydrocarbon group, and other symbols are as defined above.

Herein, Z^{2a} is preferably a nitrogen atom.

The "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by Z^4 includes the same group as the "divalent linear hydrocarbon group" of the "optionally substituted divalent linear hydrocarbon group" represented by W.

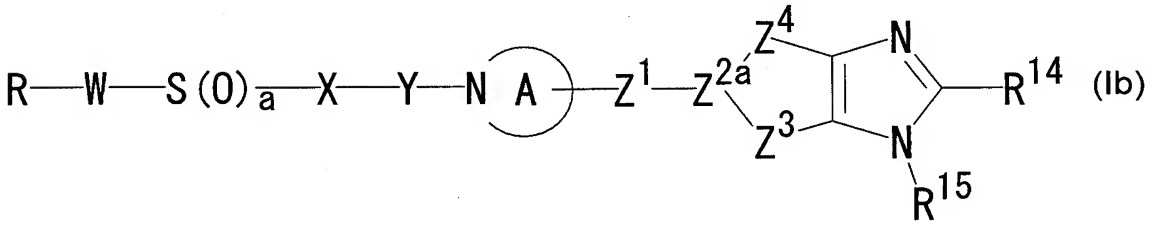
Substituents for the "optionally substituted divalent linear hydrocarbon group" represented by Z^4 include the same groups and number as those of substituents for the "optionally substituted divalent linear hydrocarbon group" represented by W.

Preferably, Z^3 and Z^4 are independently a divalent linear hydrocarbon group which may be substituted with an oxo group (preferably, C_{1-6} alkylene which may be substituted with an oxo group).

[0032]

In a preferable aspect of a compound represented by the formula (I), for example, the formula (I) is the formula (Ib):

[Chemical formula 27]



wherein R^{14} and R^{15} independently represent a hydrogen atom,

an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^{14} and R^{15} may be taken together to form an optionally substituted ring, and other symbols are as defined above.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^{14} and R^{15} includes the same group as the "hydrocarbon group" of the aforementioned "optionally substituted hydrocarbon group" represented by R^1. Substituents for "optionally substituted hydrocarbon group" include the same groups and number as those of substituents for the aforementioned "optionally substituted hydrocarbon group" represented by R^1.

Substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl group" and the "optionally substituted alkylsulfonyl group" represented by R^{14} and R^{15} include the same groups as substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl" and the "optionally substituted

alkylsulfonyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted acyl group" represented by R^{14} and R^{15} includes the same groups as the "sulfonic acid-derived acyl" and the "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally esterified carboxyl group" represented by R^{14} and R^{15} includes the same group as the "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted carbamoyl group" represented by R^{14} and R^{15} includes the same group as the "optionally substituted carbamoyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted amino group" represented by R^{14} and R^{15} includes the same group as the "optionally substituted amino" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

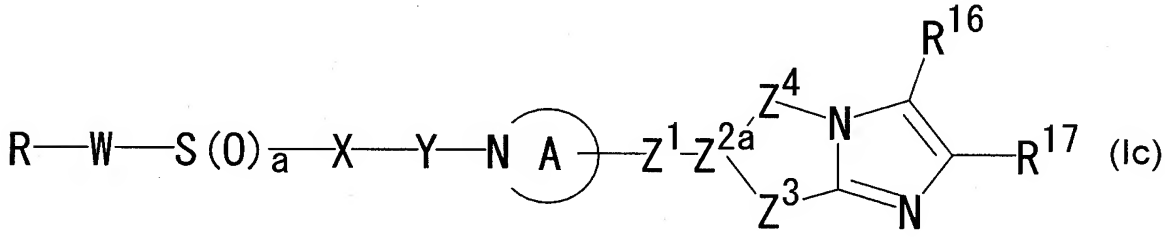
The "ring" of the "optionally substituted ring" which may be formed by binding of R^{14} and R^{15} includes the same

ring as the aforementioned "ring" formed by binding a substituent on ring B and R^1. Substituents for the "optionally substituted ring" include the same groups as substituents for the aforementioned "optionally substituted heterocyclic group" represented by R. These optional substituents may be at 1 to 5 (preferably 1 to 3) substitutable positions.

[0033]

In a preferable aspect of a compound represented by the formula (I), for example, the formula (I) is the formula (Ic):

[Chemical formula 28]



(Ic)

wherein R^{16} and R^{17} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, or R^{16} and R^{17} may be taken together to form an optionally substituted ring, and

other symbols are as defined above.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^{16} and R^{17} includes the same group as the "hydrocarbon group" of the aforementioned "optionally substituted hydrocarbon group" represented by R^1. Substituents for the "optionally substituted hydrocarbon group" include the same groups and number as those of substituents for the aforementioned "optionally substituted hydrocarbon group" represented by R^1.

Substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl group" and the "optionally substituted alkylsulfonyl group" represented by R^{16} and R^{17} include the same groups as substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl" and the "optionally substituted alkylsulfonyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R, respectively.

The "optionally substituted acyl group" represented by R^{16} and R^{17} includes the same groups as the "sulfonic acid-derived acyl" and the "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally esterified carboxyl group" represented by R^{16} and R^{17} includes the same group as the "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted carbamoyl group" represented by R^{16} and R^{17} includes the same group as the "optionally substituted carbamoyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

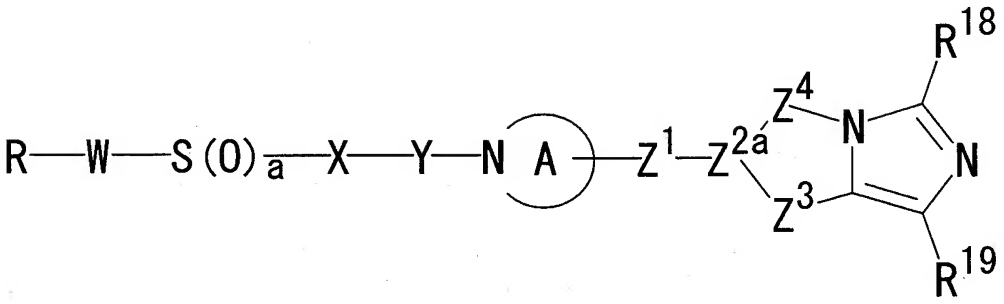
The "optionally substituted amino group" represented by R^{16} and R^{17} includes the same group as the "optionally substituted amino" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "ring" of the "optionally substituted ring" which may be formed by binding of R^{16} and R^{17} includes the same ring as the aforementioned "ring" formed by binding of a substituent on ring B and R^1. Substituents for the "optionally substituted ring" include the same group as substituents for the aforementioned "optionally substituted heterocyclic group" represented by R. These optional substituents may be at 1 to 5 (preferably 1 to 3) substitutable positions.

[0034]

In a preferable aspect of a compound represented by the formula (I), for example, the formula (I) is the formula (Id):

[Chemical formula 29]



(Id)

wherein R^{18} and R^{19} independently represent a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted acyl group, an optionally esterified carboxyl group, an optionally substituted carbamoyl group or an optionally substituted amino group, and other symbols are as defined above.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R^{18} and R^{19} includes the same group as the "hydrocarbon group" of the aforementioned "optionally substituted hydrocarbon group" represented by R^1. Substituents for the "optionally substituted hydrocarbon group" include the same groups and number as those of substituents for the aforementioned "optionally

substituted hydrocarbon group" represented by R^1.

Substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkysulfinyl group" and the "optionally substituted alkylsulfonyl group" represented by R^{18} and R^{19} include the same groups as substituents for the "optionally substituted hydroxyl group", the "optionally substituted thiol group", the "optionally substituted alkylsulfinyl" and the "optionally substituted alkylsulfonyl" exemplified as a substituent for the "optionally substituted hydrocarbon group" represented by R, respectively.

The "optionally substituted acyl group" represented by R^{18} and R^{19} includes the same groups as the "sulfonic acid-derived acyl" and the "carboxylic acid-derived acyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally esterified carboxyl group" represented by R^{18} and R^{19} includes the same group as the "optionally esterified carboxyl" exemplified as a substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted carbamoyl group" represented by R^{18} and R^{19} includes the same group as the "optionally substituted carbamoyl" exemplified as a

substituent for the "optionally substituted cyclic hydrocarbon group" represented by R.

The "optionally substituted amino group" represented by R^{18} and R^{19} includes the same group as the "optionally substituted amino" as a substituent for the aforementioned "optionally substituted cyclic hydrocarbon group" represented by R.

[0035]

In an aspect of a compound represented by the formula (I), inter alia, the formula (I) is preferably the formula (Id), and more preferably, the formula (I) is the formula (Id) and Z^{2a} is a nitrogen atom.

[0036]

In the above formulas, a indicates 0, 1 or 2 (preferably 2).

[0037]

A salt of a compound represented by the formula (I) (hereinafter, abbreviated as Compound (I) in some cases) includes pharmaceutically acceptable salts, for example, acid addition salts with acids such as trifluoroacetic acid, acetic acid, lactic acid, succinic acid, maleic acid, tartaric acid, citric acid, gluconic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, cinnamic acid, fumaric acid, phosphonic acid, hydrochloric acid, nitric acid, hydrobromic acid, hydriodic acid,

sulfamic acid, sulfuric acid and the like, metal salts such as sodium, potassium, magnesium, calcium and the like, and organic salts such as trimethylamine, triethylamine, pyridine, picoline, N-methylpyrrolidine, N-methylpiperidine, N-methylmorpholine and the like.

A prodrug of Compound (I) refers to a compound which is converted into Compound (I) by a reaction due to an enzyme or gastric acid under the physiological condition in a living body, that is, a compound which is changed into Compound (I) by enzymatic oxidation, reduction, hydrolysis or the like, or a compound which is changed into Compound (I) by hydrolysis with gastric acid. A prodrug of Compound (I) includes a compound obtained by acylating, alkylating or phosphorylating the amino group of Compound (I) (e.g. a compound obtained by eicosanoylating, alanylating, pentylaminocarbonylating, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylating, tetrahydrofuranylating, pyrrolidylmethylating, pivaloyloxymethylating or tert-butylating the amino group of Compound (I)), a compound obtained by acylating, alkylating, phosphorylating or borating the hydroxyl group of Compound (I) (e.g. a compound obtained by acetylating, palmitoylating, propanoylating, pivaloylating, succinylating, fumarylating, alanylating or dimethylaminomethylcarbonylating the hydroxyl group of Compound (I)) and a compound obtained by

esterifying or amidating the carboxyl group of Compound (I) (e.g. a compound obtained by ethylesterifying, phenylesterifying, carboxymethylesterifying, dimethylaminomethylesterifying, pivaloyloxymethylesterifying, ethoxycarbonyloxyethylesterifying, phthalidylesterifying, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterifying, cyclohexyloxycarbonylethylesterifying or methylamidating the carboxyl group of Compound (I)). These compounds can be prepared from Compound (I) by a known method per se.

A prodrug of Compound (I) may be also a compound which is changed into Compound (I) under the physiological condition as described in "Development of Medicaments", vol. 7, Molecular Design, p.163-198 published by HIROKAWASHOTEN in 1990.

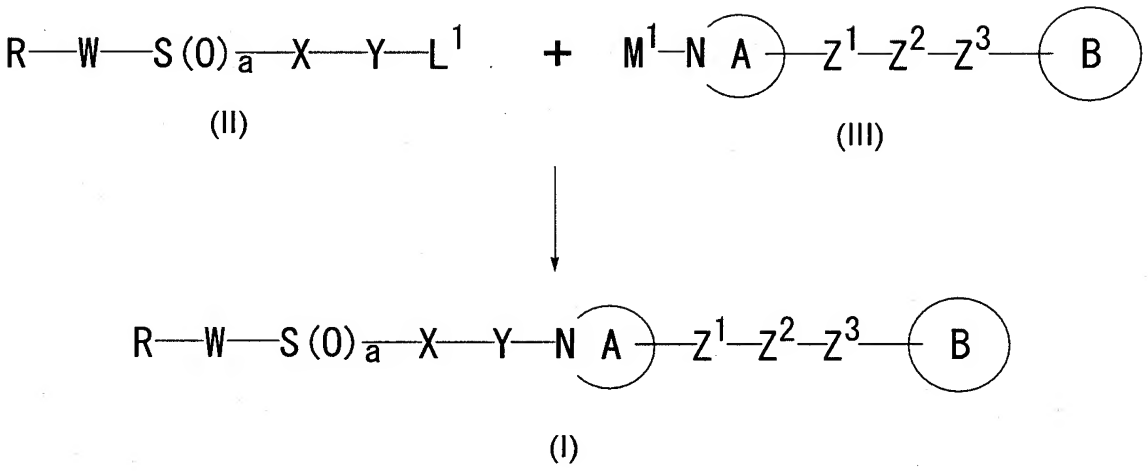
Compound (I) may be labeled with an isotope (e.g. ^{3}H, ^{14}C, ^{35}S, ^{125}I) or the like.

[0038]

Compound (I) or a salt thereof can be prepared, for example, by the following methods (A) to (E). Each compound described in the following schemes may form a salt as far as it does not inhibit the reaction. Such a salt includes the same salts as those of Compound (I).

Method A:

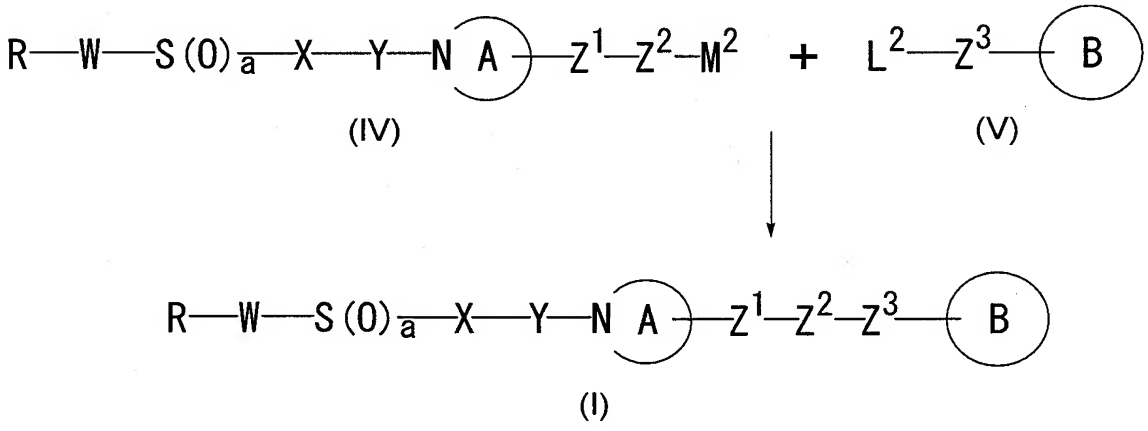
[Chemical formula 30]



[0039]

Method B

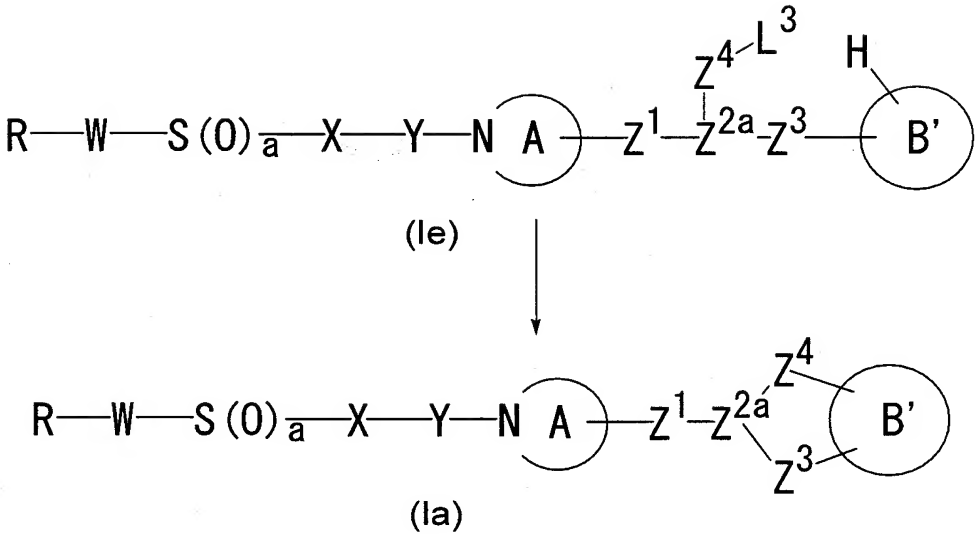
[Chemical formula 31]



[0040]

Method C

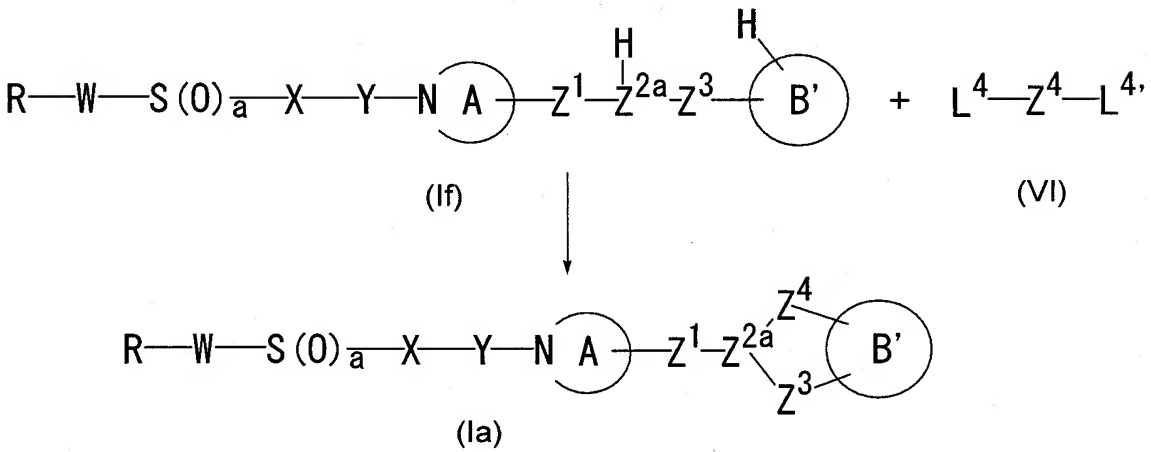
[Chemical formula 32]



[0041]

Method D

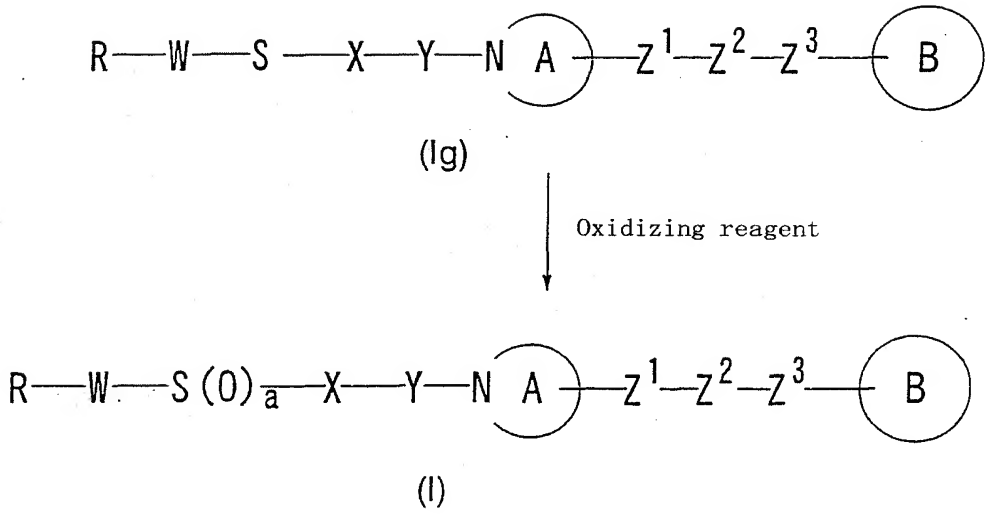
[Chemical formula 33]



[0042]

Method E

[Chemical formula 34]

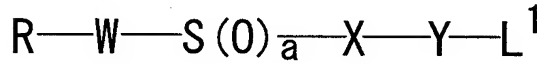


[0043]

Method A

Compound (I) can be prepared by reacting Compound (II) represented by the formula (II):

[Chemical formula 35]

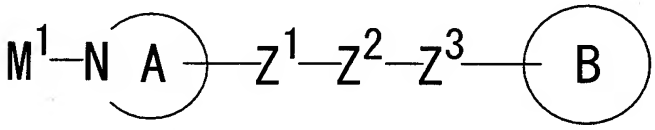


(II)

wherein L^1 represents a leaving group (e.g. a group forming free carboxylic acid, a salt thereof (inorganic salt, organic salt etc.) or a reactive derivative thereof (e.g. acid halide, ester, acid azide, acid anhydride, mixed acid anhydride, active amide, active ester, active thioester etc.), such as a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), C_{1-6} alkylsulfonyloxy group optionally substituted with 1 to 3 halogen atoms (e.g.

methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy etc.), an optionally substituted arylsulfonyloxy group (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy etc.) or a hydroxyl group), and other symbols are as defined above, (in particular, Compound (II) wherein L^1 is a hydroxyl group is referred to as free acid (II')), with Compound (III) represented by the formula (III):

[Chemical formula 36]



(III)

wherein M^1 represents a hydrogen atom, an alkaline metal (e.g. lithium, sodium, potassium, cesium etc.), an alkaline earth metal (e.g. magnesium, calcium etc.) or a leaving group (e.g. trimethylsilyl group), and other symbols are as defined above.

Alternatively, Compound (I) can be prepared by reacting Compound (III) or a salt thereof with free acid (II') or a salt thereof (inorganic salt, organic salt etc.) or a derivative thereof (e.g. acid halide, ester, acid azide, acid anhydride, mixed acid anhydride, active amide, active ester, active thioester etc.). A salt of Compound (III) includes acid addition salts with the above-mentioned acids which may form an acid addition salt with Compound (I).

An inorganic salt of Compound (II) includes an alkaline metal salt (e.g. lithium salt, sodium salt, potassium salt, cesium salt etc.), and an alkaline earth metal salt (e.g. magnesium salt, calcium salt etc.). An organic salt of Compound (II) includes a trimethylamine salt, a triethylamine salt, a tert-butyldimethylamine salt, a dibenzylmethylamine salt, a benzyldimethylamine salt, a N,N-dimethylaniline salt, a pyridine salt, a quinoline salt and the like. Acid halide includes acid chloride, acid bromide and the like. Ester includes lower alkyl esters such as methyl, ethyl and the like. A mixed acid anhydride includes a mono C_{1-4} alkylcarbonic acid mixed acid anhydride (e.g. a mixed acid anhydride of free acid (II') with monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, monoisobutyl carbonate, mono-tert-butyl carbonate, monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate etc.), a C_{1-6} aliphatic carboxylic acid mixed acid anhydride (e.g. a mixed acid anhydride of free acid (II) with acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid etc.), a C_{7-11} aromatic carboxylic acid mixed acid anhydride (e.g. a mixed acid anhydride of free acid (II') with benzoic acid, p-toluic acid, p-chlorobenzoic acid

etc.), an organic sulfonic acid mixed acid anhydride (e.g. a mixed acid anhydride with methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid etc.) and the like. Active amide includes amide with a nitrogen-containing heterocyclic compound (e.g. acid amide of free acid (II') with pyrazole, imidazole, benzotriazole etc., and these nitrogen-containing heterocyclic compounds may be substituted with C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy etc.), a halogen atom (e.g. fluorine, chlorine, bromine etc.), oxo, thioxo, C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio etc.), etc.) and the like.

Active ester includes, in addition to organic phosphoric acid ester (e.g. diethoxyphosphoric acid ester, diphenoxyphosphoric acid ester etc.), p-nitrophenyl ester, 2,4-dinitrophenyl ester, cyanomethyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, 6-chloro-1-hydroxybenzotriazole ester, 1-hydroxy-1H-2-pyridone ester and the like. Active thioester includes esters with aromatic heterocyclic thiol compounds [these heterocyclic rings may be substituted with C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-

butyl, tert-butyl etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy etc.), a halogen atom (e.g. fluorine, chlorine, bromine etc.), C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, butylthio etc.) etc.] (e.g. 2-pyridylthiol ester, 2-benzothiazolylthiol ester) and the like.

This reaction is generally performed in a solvent and, if needed, in the presence of a base or a condensing agent (e.g. carbodiimides such as DCC, WSC, DIC etc.), phosphoric acid derivative (e.g. diethyl cyanophosphate, DPPA, DOP-Cl etc.), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM:Kunishima et al., Tetrahedron, 1999, 55, 13159) or the like.

As a solvent, a solvent which does not inhibit the reaction is appropriately selected and, for example, alcohols (e.g. methanol, ethanol, propanol, isopropanol, butanol, tert-butanol etc.), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol-dimethyl ether etc.), esters (e.g. ethyl formate, ethyl acetate, n-butyl acetate etc.), carboxylic acids (e.g. formic acid, acetic acid, propionic acid etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, chlorobenzene etc.), hydrocarbons (e.g. n-hexane, benzene, toluene etc.), amides

(e.g. formamide, N,N-dimethylformamide, N,N-dimethylacetamide etc.), ketones (e.g. acetone, methyl ethyl ketone, methyl isobutyl ketone etc.), nitriles (e.g. acetonitrile, propionitrile etc.) and, additionally, dimethyl sulfoxide, sulfolane, hexamethylphosphoramide, water and the like are used alone or as a mixed solvent.

A base includes inorganic bases such as lithium hydroxide, potassium hydroxide, sodium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like; C_{1-6} lower fatty acid alkaline metal salts such as sodium formate, sodium acetate, potassium acetate and the like; and tertiary amines such as triethylamine, tri(n-propyl)amine, tri(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like.

In this reaction, 0.5 to 5 equivalents, preferably 0.8 to 2 equivalents of Compound (III) is used based on the amount of Compound (II).

The reaction temperature is -50 to 150°C, preferably -20 to 100°C.

The reaction time varies depending on the kind of Compound (II) or (III), the kinds of a solvent and a base, the reaction temperature and the like. It is usually 1

minute to about 100 hours, preferably about 15 minutes to about 48 hours.

[0044]

Method B

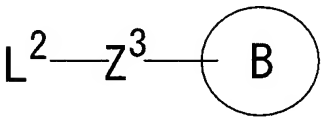
Compound (I) can be prepared by reacting Compound (IV) represented by the formula (IV):

[Chemical formula 37]

(IV)

wherein M^2 represents a hydrogen atom, an alkaline metal (e.g. lithium, sodium, potassium, cesium etc.), an alkaline earth metal (e.g. magnesium, calcium etc.) or a leaving group (e.g. trimethylsilyl group etc.), and other symbols are as defined above, or a salt thereof with Compound (V) represented by the formula (V):

[Chemical formula 38]



(V)

wherein L^2 represents a leaving group (e.g. a halogen atom (e.g. fluorine, chlorine, bromine, iodine etc.), a C_{1-6} alkylsulfonyloxy group optionally substituted with 1 to 3 halogen atoms (e.g. methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy etc.), an optionally substituted arylsulfonyloxy group (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, p-bromobenzenesulfonyloxy etc.) or a

formyl group, and other symbols are as defined above, or a salt thereof. A salt of Compound (IV) or (V) includes acid addition salts with the aforementioned acids which may form acid addition salts with Compound (I).

This reaction is generally performed in a solvent, and a solvent which does not inhibit the reaction is appropriately selected. A solvent and a base used in this reaction are the same as those described for Method A.

When L^2 is a formyl group, the reaction is performed in the presence of a reducing agent (e.g. sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, diborane, diborane-tetrahydrofuran complex, diborane-dimethyl sulfide complex etc.). Such a reducing agent is used in an amount of 0.5 to 10 equivalents, preferably 0.8 to 5 equivalents based on the amount of Compound (V).

In this reaction, 0.5 to 5 equivalents, preferably 0.8 to 2 equivalents of Compound (IV) is used based on the amount of Compound (V).

The reaction temperature is -20 to 200°C, preferably -5 to 170°C.

The reaction time varies depending on the kind of Compound (IV) or (V), the kind of a solvent, the reaction temperature and the like. It is usually about 1 minute to about 72 hours, preferably about 15 minutes to about 24

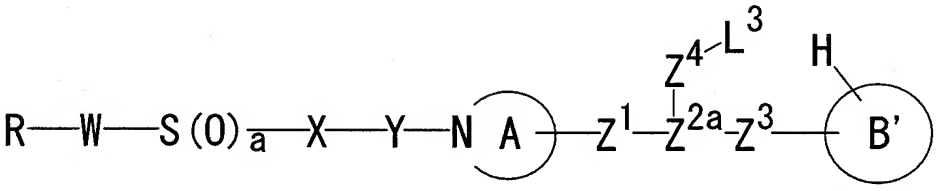
hours.

[0045]

Method C

Compound (Ia) can be prepared by reacting Compound (Ie) represented by the formula (Ie):

[Chemical formula 39]



(Ie)

wherein L^3 represents a leaving group and other symbols are as defined above, or a salt thereof with a base.

The leaving group represented by L^3 includes the same group as that represented by L^1.

A salt of Compound (Ie) includes acid addition salts with the aforementioned acids which may form acid addition salts with Compound (I).

A base used in this reaction includes the same base as that described for Method A.

This reaction is generally performed in a solvent, if needed, in the presence of a condensing agent. A solvent and a condensing agent are the same as those described for Method A, respectively.

In this reaction, 0.5 to 5 equivalents, preferably 0.8 to 2 equivalents of a base is used based on the amount of Compound (Ie).

The reaction temperature is -50 to 150°C, preferably -20 to 100°C.

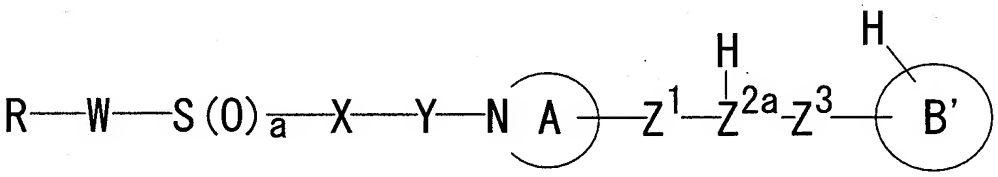
The reaction time varies depending on the kind of Compound (Ie) or a base, the kind of a solvent, the reaction temperature. It is usually about 1 minute to about 100 hours, preferably about 15 minutes to about 48 hours.

[0046]

Method D

Compound (Ia) or a salt thereof can be prepared by reacting Compound (If) represented by the formula (If):

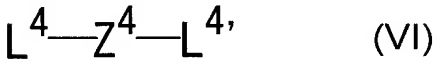
[Chemical formula 40]



(If)

wherein symbols are as defined above, or a salt thereof with a compound represented by the formula (VI):

[Chemical formula 41]



(VI)

wherein L^4 and $L^{4'}$ represent a leaving group, and other symbols are as defined above.

This method can be performed by reacting Compound (If) or a salt thereof (inorganic salt, organic salt etc.) with Compound (VI).

A salt of Compound (If) includes acid addition salts

with the aforementioned acids which may form acid addition salts with Compound (I).

In Compound (VI), the leaving group represented by L^4 and $L^{4'}$ includes the same group as that represented by L^1.

When Z^4 is -CO-, as Compound (VI), a carbonylating reagent is used. A carbonylating reagent includes carbonyldiimidazole, phosgene, diphosgene, triphosgene, dialkyl carbonate (e.g. methyl carbonate, diethyl carbonate etc.) and the like.

The reaction of this method is generally performed in a solvent, and a solvent which does not inhibit the reaction is appropriately selected. As such the solvent, alcohols (e.g. methanol, ethanol, propanol, isopropanol, butanol, tert-butanol etc.), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol-dimethyl ether etc.), esters (e.g. ethyl formate, ethyl acetate, n-butyl acetate etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, trichlene, 1,2-dichloroethane etc.), hydrocarbons (e.g. n-hexane, benzene, toluene etc.), amides such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like, nitriles such as acetonitrile, propionitrile and the like and, additionally, dimethyl sulfoxide, sulfolane, hexamethylphosphoramide, water and the like are used alone

or as a mixed solvent.

This reaction may be also performed in the presence of a base. Such a base includes inorganic bases such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and the like, and tertiary amines such as triethylamine, tri(n-propyl)amine, tri(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, diazabicycloundecane, diazabicycloundecene and the like.

In this reaction, 0.5 to 10 equivalents, preferably 0.8 to 3 equivalents of Compound (VI) is used based on the amount of Compound (If).

The reaction temperature is -30 to 250°C, preferably -10 to 100°C.

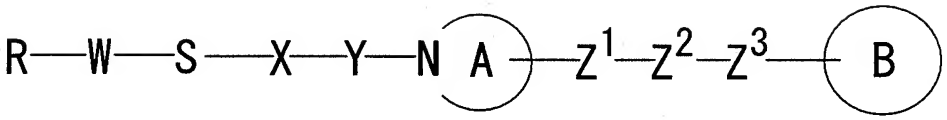
The reaction time varies depending on the kinds of Compound (If) and (VI), the kind of a solvent, the reaction temperature and the like. It is usually about 1 minute to about 72 hours, preferably about 15 minutes to about 24 hours.

[0048]

Method E

Compound (I) can be prepared by oxidizing Compound (Ig) represented by the formula (Ig):

[Chemical formula 42]



(Ig)

wherein symbols are as defined above, or a salt thereof.

This oxidization reaction is performed in the presence of an oxidizing agent. An oxidizing agent includes oxygen, hydrogen peroxide, organic peracids such as perbenzoic acid, m-chloroperbenzoic acid, peracetic acid, perchlorates such as lithium perchlorate, silver perchlorate, tetrabutylammonium perchlorate and the like, periodates such as sodium periodate, periodic acid, manganese dioxide, lead tetraacetate, permanganates such as potassium permanganate, halogen such as iodine, bromine, chlorine and the like, N-bromosuccinimide, N-chlorosuccinimide, sulfuryl chloride, chloramine T and the like.

This reaction is generally performed in a solvent, and a solvent which does not inhibit the reaction is appropriately selected. As such the solvent, alcohols (e.g. methanol, ethanol, propanol, isopropanol, butanol, tert-butanol etc.), ethers (e.g. dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol-dimethyl ether etc.), esters (e.g. ethyl formate, ethyl acetate, n-butyl acetate etc.), carboxylic acids (e.g. formic acid, acetic acid, propionic acid etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform,

carbon tetrachloride, trichloroethylene, 1,2-dichloroethane, chlorobenzene etc.), hydrocarbons (e.g. n-hexane, benzene, toluene etc.), amides (e.g. formamide, N,N-dimethylformamide, N,N-dimethylacetamide etc.), ketones (e.g. acetone, methyl ethyl ketone, methyl isobutyl ketone etc.), nitriles (e.g. acetonitrile, propionitrile etc.) and, additionally, sulfolane, hexamethyl phosphoramide, water and the like are used alone or as a mixed solvent.

This reaction can be also performed in the presence of a base. A base includes inorganic bases, for example, alkaline metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, alkaline earth metal hydroxides such as magnesium hydroxide and potassium hydroxide, alkaline metal carbonates such as sodium carbonate and potassium carbonate, and alkaline metal hydrogencarbonates such as sodium hydrogencarbonate and potassium hydrogencarbonate.

In this reaction, an oxidizing agent is used in an amount of 0.1 to 20 equivalents (preferably about 0.4 to 10 equivalents) and a base is used in an amount of 0.1 to 20 equivalents (preferably 0.4 to 10 equivalents), based on the amount of Compound (Ia).

In addition, this reaction may be performed in the presence of an acid as necessary. Such acid includes mineral acids such as hydrochloric acid, hydrobromic acid,

sulfuric acid, phosphoric acid, perchloric acid and the like, sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, camphorsulfonic acid and the like, and organic acids such as formic acid, acetic acid, propionic acid, trifluoroacetic acid and the like. Such acid is used in an amount of 0.1 to 20 equivalents, preferably 0.5 to 10 equivalents based on the amount of Compound (Ia).

The reaction temperature is about -10°C to about 250°C, preferably about -5°C to about 150°C.

The reaction temperature varies depending on the kinds of Compound (Ia), a base and a solvent, the reaction temperature and the like. It is usually about 1 minute to about 50 hours, preferably about 5 minutes to about 24 hours.

[0049]

Starting materials and intermediates used in the above respective reactions are prepared by applying or adapting a known method, for example, methods described in Examples or apparently chemically equivalent methods thereof, or by a method of the present invention.

The Compound (I) thus obtained can be isolated and purified from the reaction mixture by a known means per se, for example, means such as extraction, concentration, neutralization, filtration, recrystallization, column

chromatography, thin layer chromatography and the like.

A salt of Compound (I) can be prepared by a known means per se, for example, by addition of an inorganic or organic acid to Compound (I).

When optical isomers of Compound (I) may be present, individual optical isomers and a mixture thereof are included in the scope of the present invention and, if desired, these isomers may be optically resolved according to a known means per se, or may be prepared individually.

In addition, Compound (I) or a salt thereof may be a hydrate, and both of a hydrate and a non-hydrate are included in the scope of the present invention.

[0050]

Since Compound (I) or a salt thereof of the present invention is low toxic and safe, inhibits FXa and has anti-coagulation activity, it is useful for preventing or treating, for example, myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary thromboembolism, economy class syndrome, thromboembolism during or after an operation, inflammation, cancer, and the like, and the following diseases in animals especially in mammals (e.g., human, monkey, cat, swine, horse, bovine, mouse, rat, guinea pig, dog, rabbit and the like), and among them, it is preferably used for preventing or treating cardiogenic cerebral embolism due to atrial

fibrillation, and cerebral infarction due to embolism caused by arteriosclerosis such as that of the carotid, deep venous thrombosis, pulmonary thromboembolism and the like.

Brain:

Cerebral infarction, cerebral embolism caused by atrial fibrillation, acute ischemic cerebral apoplexy, acute stage cerebral thrombosis, cerebrovascular contraction after subarachnoid hemorrhage, Alzheimer's disease, transient ischemic attack (TIA), mixed dementia, cerebrovascular dementia, asymptomatic/multiple cerebral infarction, combination use or supplemental use with a thrombolytic agent against cerebral thrombosis.

Heart:

Acute coronary disease such as acute myocardial infarction, myocardial infarction, unstable angina, prognosis improvement or secondary onset prevention of acute coronary disease such as angina, acute heart failure, congestive chronic heart failure, vascular reocclusion and restenosis after coronary intervention such as stent indwelling or PTCA (percutaneous transluminal coronary angioplasty) or atherectomy, combination use or supplemental use with a thrombolytic agent against acute coronary disease.

Periphery:

Deep venous thrombosis, prevention or secondary onset prevention of deep venous thrombosis, chronic arterial obliterans, peripheral vascular disease such as arteriosclerotic obliterans, adult respiratory distress syndrome, acute renal failure, chronic renal disease (e.g. diabetic nephropathy, chronic glumerular nephritis, IgA nephropathy etc.), diabetic circulation disorder, pain, nerve disorder, diabetic complication such as diabetic retinopathy and the like.

Others:

Thrombocytopenia caused by dialysis, thrombocytopenia on a major operation, disseminated intravascular coagulation syndrome (DIC) developed in a patient suffering from progression of arteriosclerosis or cancer metastasis or systemic inflammatory reaction syndrome (SIRS) or pancreatitis or cancer or leukemia or a major operation or sepsis or the like, various organ disorders such as liver function disorder caused by oligemia or ischemia or retention of blood, various organ failures caused by progression of shock or DIC (e.g. lung failure, liver failure, kidney failure, heart failure etc.), prevention of perfusion blood coagulation during blood extracorporeal circulation, substitute therapeutic use against development of thrombocytopenia caused by heparin administration, promotion of bedsore or wound healing, inhibition of

activation of blood excessive coagulation reaction on various hormone supplement therapy, substitute therapeutic use for a patient resistant or contraindicative to warfarin.

[0051]

Compound (I) of the present invention or a salt thereof can be orally or parenterally administered as it is or as a composition comprising a pharmacologically acceptable carrier.

An oral dosage form of a pharmaceutical composition containing Compound (I) of the present invention or a salt thereof includes a tablet (including a sugar-coated tablet, a film coating tablet), a pill, a granule, powder, a capsule (including a soft capsule, a microcapsule), syrup, emulsion and suspension. A parenteral dosage form of a pharmaceutical composition containing Compound (I) of the present invention or a salt thereof includes an injection, an infusion, a drip and a suppository. It is also advantageous that Compound (I) of the present invention or a salt thereof in combination with an appropriate base (e.g. a polymer of butyric acid, a polymer of glycolic acid, a copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.) is formulated into a sustained release form.

The content of Compound (I) or a salt thereof in a

pharmaceutical composition of the present invention varies depending on the form of a composition, and is usually 2 to 85% by weight, preferably 5 to 70% by weight of the total composition.

[0052]

Compound (I) or a salt thereof may be formulated into the aforementioned dosage forms by known methods used generally in the art. When Compound (I) or a salt thereof is formulated into the aforementioned dosage forms, if necessary, appropriate amounts of an excipient, a binder, a disintegrant, a lubricant, a sweetener, a surfactant, a suspending agent, an emulsifying agent and the like which are conventionally used in pharmaceutical field may be added.

For example, when Compound (I) or a salt thereof is formulated into a tablet, an excipient, a binder, a disintegrant, a lubricant and the like are added. When Compound (I) or a salt thereof is formulated into a pill or a granule, an excipient, a binder, a disintegrant and the like are added. When Compound (I) or a salt thereof is formulated into powder or a capsule, an excipient and the like are added. When Compound (I) or a salt thereof is formulated into syrup, a sweetener and the like are added. When Compound (I) or a salt thereof is formulated into an emulsion or a suspension, a suspending agent, a surfactant,

an emulsifying agent and the like are added.

[0053]

An excipient includes lactose, white sugar, glucose, starch, sucrose, microcrystalline cellulose, licorice powder, mannitol, sodium hydrogencarbonate, calcium phosphate, calcium sulfate and the like.

A binder includes 5 to 10% by weight starch paste, a 10 to 20% by weight gum arabic solution or gelatin solution, a 1 to 5% by weight tragacanth solution, a carboxymethylcellulose solution, a sodium alginate solution, glycerin and the like.

A disintegrant includes starch, calcium carbonate and the like.

A lubricant includes magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

A sweetener includes glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

A surfactant includes sodium lauryl sulfate, Polysorbate 80, sorbitan monofatty acid ester, polyoxyl stearate 40 and the like.

A suspending agent includes gum arabic, sodium alginate, sodium carboxymethylcellulose, methylcellulose, bentonite and the like.

An emulsifying agent includes gum arabic, tragacanth, gelatin, Polysorbate 80 and the like.

Further, when Compound (I) or a salt thereof is formulated into the aforementioned dosage forms, if desired, appropriate amounts of a coloring agent, a preservative, a flavor, a corrigent, a stabilizer, a thickener and the like which are conventionally used in pharmaceutical field may be added.

[0054]

A pharmaceutical composition of the present invention containing Compound (I) or a salt thereof is safe and low toxic and can be used safely. A daily dose of a pharmaceutical composition of the present invention varies depending on the condition and body weight of a patient, the kind of a compound, an administration route and the like. For example, when it is administered orally to an adult patient (body weight about 60 kg) with thrombosis, the daily dose is about 1 to 1000 mg, preferably about 3 to 500 mg, more preferably about 10 to 350 mg of an active ingredient (Compound (I) or a salt thereof), which may be administered once or in two or three divided portions.

When Compound (I) or a salt thereof of the present invention is administered parenterally, it may be usually administered as a form of a solution (e.g. an injection). A dose per time varies depending on a subject to be administered, an organ to be targeted, symptom, an administration method and the like. For example,

conveniently, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg per kg body weight of Compound (I) or a salt thereof is administered intravenously in a dosage form of an injection. An injection includes, in addition to intravenous injection, subcutaneous injection, intradermal injection, intramuscular injection, drip injection and the like. A long-acting preparation includes an iontophoresis transdermal agent. Such an injection is prepared by a known method per se, that is, by dissolving, suspending or emulsifying Compound (I) or a salt thereof of the present invention in a sterile aqueous or oily liquid. An aqueous liquid for injection includes physiological saline, and an isotonic solution containing glucose and other supplemental agent (e.g. D-sorbitol, D-mannitol, sodium chloride etc.) and may be used in combination with a suitable solubilizer, for example, alcohol (e.g. ethanol), polyalcohol (e.g. propylene glycol, polyethylene glycol) or a nonionic surfactant (e.g. Polysorbate 80, HCO-50). An oily liquid for injection includes sesame oil and soybean oil and may be used in combination with a solubilizer such as benzyl benzoate or benzyl alcohol. In addition, a buffer (e.g. phosphate buffer, sodium acetate buffer), a soothing agent (e.g. benzalkonium chloride, procaine hydrochloride etc.), a stabilizer (e.g. human serum albumin, polyethylene glycol

etc.), a preservative (e.g. benzyl alcohol, phenol etc.) and the like may be added. The injection thus obtained is usually filled in an ampule.

The pharmaceutical composition of the present invention can be appropriately used in combination with a drug (hereinafter, abbreviated as a concomitant drug) such as a thrombolytic agent (e.g. TPA, urokinase etc.), an Alzheimer's disease treating drug (e.g. Avan, Calan etc.), a cholesterol treating drug (e.g. an HMG-CoA reductase inhibitor such as simvastatin, pravastatin etc.), a TG lowering drug (e.g. clofibrate etc.), an AII antagonist (e.g. candesartan cilexetil, losartan etc.), an anti-platelet drug (e.g. clopidogrel, abciximab, aspirin etc.), a Ca antagonist (e.g. Calslot, amlodipine etc.), an ACE inhibitor (e.g. enalapril, captopril etc.), a β blocker (e.g. metoprolol, carvedilol etc.) or an antiarrhythmic drug (e.g. procaine amide etc.). The concomitant drug may be a low-molecular compound, a high-molecular protein, a polypeptide, an antibody, or a vaccine. An administration mode of the compound of the present invention and a concomitant drug is not limited particularly, as long as the compound of the present invention and the concomitant drug are combined upon administration. For example, such an administration mode includes (1) administration of a single preparation obtained by formulating the compound of

the present invention and a concomitant drug simultaneously, (2) simultaneous administration of two kinds of preparations obtained by formulating the compound of the present invention and a concomitant drug separately, via a single administration route, (3) separate administration at an interval of two kinds of preparations obtained by formulating the compound of the present invention and a concomitant drug separately, via a single administration route, (4) simultaneous administration of two kinds of preparations obtained by formulating the compound of the present invention and a concomitant drug separately, via different administration routes, and (5) separate administration at an interval of two kinds of preparations obtained by formulating the compound of the present invention and a concomitant drug separately, via different administration routes (e.g. administration of the compound of the present invention followed by the concomitant drug, or administration in the reverse order). The dose of a concomitant drug can be selected appropriately on the basis of a dose clinically used. In addition, a combination ratio of the compound of the present invention and a concomitant drug can be selected appropriately depending on a subject to be administered, an administration route, a disease to be treated, symptom, and a combination thereof. For example, when a subject to be administered is a human,

0.01 to 100 parts by weight of a concomitant drug may be used based on 1 part by weight of the compound of the present invention.

[0055]

Embodiment for Performing the Invention

The present invention is further illustrated by the following Examples, Formulation Examples and Experimental Examples which are merely examples and do not limit the present invention, and various changes may be made without departing from the scope of the present invention.

In Examples, elution of column chromatography was confirmed under observation with TLC (Thin Layer Chromatography). For TLC observation, $60F_{254}$ manufactured by Merck or NH manufactured by Fuji Silysia Chemical Ltd. as a TLC plate, a solvent used as an eluting solvent in column chromatography as a developing solvent, and a UV detector as a detection method were used. As a silica gel for a column, Kiesel Gel 60 (70 to 230 mesh) or Kiesel Gel 60 (230 to 400 mesh) manufactured by Merck was used. As a basic silica gel for a column, basic silica NH-DM1020 (100 to 200 mesh) manufactured by Fuji Silysia Chemical Ltd. was used. NMR spectrum was measured with a Varian Gemini 200-type or 300-type spectrometer using tetramethylsilane as an internal or external standard, and chemical shift was expressed as δ value and a coupling constant was expressed

as Hz. IR spectrum was measured with Shimadzu FTZR-8200-type spectrometer. A numerical value shown within ( ) for a mixed solvent is a mixing ratio by volume of each solvent. In addition, % for a solution shows the amount (gram) of a solute in 100 ml of a solution. In addition, symbols used in Examples have the following meanings.

s: singlet

d: doublet

t: triplet

q: quartet

dd: double doublet

m: multiplet

br: broad

brs: broad singlet

J: coupling constant

WSC: water-soluble carbodiimide

THF: tetrahydrofuran

DMF: N,N'-dimethylformamide

DMSO: dimethyl sulfoxide

HOBt: 1-hydroxybenztriazole

[0056]

Examples

Example 1

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-1-yl)piperidine hydrochloride

Tert-butyl 4-(1H-imidazol-1-yl)piperidine-1-carboxylic acid (JP-A 7-501556) (0.28 g) was dissolved in 40% hydrogen chloride ethanol (4 mL) and ethanol (5 mL) and stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and then subjected to azeotropic distillation with ethanol. The residue was washed with diisopropyl ether to obtain a solid, which was dissolved in acetonitrile (15 mL) together with DBU (0.34 g) and triethylamine (0.34 g). This solution was added to a suspension of 3-[(6-chrolo-2-naphthyl)sulfonyl]propionic acid (0.33 g), HOBt(0.26 g) and WSC (0.32 g) in acetonitrile (15 mL), and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure and diluted with ethyl acetate and an aqueous potassium carbonate solution. An organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate) to obtain the title compound (0.40 g, 83%) as pale yellow gum.

NMR (300 MHz, $CDCl_3$) δ: 1.70-1.92 (2H, m), 2.09-2.22 (2H, m), 2.64-2.72 (1H, m), 2.90-2.97 (2H, m), 3.17-3.25 (1H, m), 3.54-3.61 (2H, m), 4.00-4.09 (1H, m), 4.08-4.21 (1H, m), 4.69-4.73 (1H, m), 6.93 (1H, t, J = 1.2), 7.08 (1H, d, J = 1.2), 7.54 (1H, s), 7.60 (1H, dd, J = 8.7 and 2.1), 7.93-

7.97 (4H, m), 8.49 (1H, d, J = 1.2).

Elemental analysis for $C_{21}H_{22}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 57.20; H, 5.26; N, 9.53

Found (%): C, 57.42; H, 5.46; N, 9.47

[0057]

Example 2

1-{3-[(6-Bromo-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-1-yl)piperidine

From 3-[(6-bromo-2-naphthyl)sulfonyl]propionic acid (0.38 g), the title compound (0.27 g, 51%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.71-1.90 (2H, m), 2.08-2.22 (2H, m), 2.64-2.72 (1H, m), 2.90-2.97 (2H, m), 3.17-3.25 (1H, m), 3.54-3.61 (2H, m), 4.00-4.04 (1H, m), 4.09-4.21 (2H, m), 4.68-4.73 (1H, m), 6.93 (1H, d, J = 1.2), 7.09 (1H, s), 7.54 (1H, s), 7.73 (1H, dd, J = 8.8 and 2.0), 7.86-7.97 (3H, m), 8.14 (1H, d, J = 1.8), 8.48 (1H, s).

Elemental analysis for $C_{21}H_{22}BrN_3O_3S \cdot 0.7H_2O$

Calculated (%): C, 51.58; H, 4.82; N, 8.59

Found (%): C, 51.47; H, 4.85; N, 8.56

[0058]

Example 3

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-methyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2-methyl-1H-imidazol-1-

yl)piperidine-1-carboxylic acid (JP-A 7-501556)(0.27 g), the title compound (0.37 g, 83%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.68-1.84 (2H, m), 1.97-2.09 (2H, m), 2.42 (3H, s), 2.61-2.69 (1H, m), 2.91-2.98(2H, m), 3.15-3.24 (1H, m), 3.54-3.62 (2H, m), 4.02-4.13 (2H, m), 4.73-4.77 (1H, m), 6.81 (1H, d, J = 1.5), 6.94 (1H, d, J = 1.5), 7.60 (1H, dd, J = 8.9 and 2.0), 7.91-7.97 (4H, m), 8.50 (1H, s).

Elemental analysis for $C_{22}H_{24}ClN_3O_3S \cdot 0.9H_2O$

Calculated (%): C, 57.17; H, 5.63; N, 9.09

Found (%): C, 57.28; H, 5.71; N, 9.16

[0059]

Example 4

1-{3-[(6-Bromo-2-naphthyl)sulfonyl]propanoyl}-4-(2-methyl-1H-imidazole-1-yl)piperidine

From tert-butyl 4-(2-methyl-1H-imidazol-1-yl)piperidine-1-carboxylate (JP-A 7-501556) (0.27 g) and 3-[(6-bromo-2-naphthyl)sulfonyl]propionic acid (0.34 g), the title compound (0.47 g, 96%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.69-1.85 (2H, m), 1.97-2.08 (2H, m), 2.42 (3H, s), 2.65 (1H, t, J = 12.1), 2.91-2.98 (2H, m), 3.16-3.25 (1H, m), 3.54-3.62 (2H, m), 4.02-4.11 (2H, m), 4.74-4.77 (1H, m), 6.81 (1H, d, J = 1.5), 6.94 (1H, d, J =

1.5), 7.73 (1H, dd, J = 8.9 and 1.9), 7.87-7.95 (3H, m), 8.14 (1H, s), 8.48 (1H, s).

Elemental analysis for $C_{22}H_{24}BrN_3O_3S \cdot 0.7H_2O$

Calculated (%): C, 52.53; H, 5.09; N, 8.35

Found (%): C, 52.34; H, 5.30; N, 8.19

[0060]

Example 5

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(4-methyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(4-methyl-1H-imidazol-1-yl)piperidine-1-carboxylate (JP-A 7-501556) (0.39 g), the title compound (0.41 g, 70%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.74-1.95 (2H, m), 2.12-2.27 (2H, m), 2.21 (3H, d, J = 0.8), 2.60-2.72 (1H, m), 2.89-2.97 (2H, m), 3.12-3.24 (1H, m), 3.53-3.62 (2H, m), 3.96-4.14 (2H, m), 4.65-4.72 (1H, m), 6.63 (1H, s), 7.41 (1H, d, J = 1.0), 7.60 (1H, dd, J = 8.8 and 1.8), 7.93-7.97 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{22}H_{24}ClN_3O_3S \cdot 0.9H_2O$

Calculated (%): C, 58.08; H, 5.54; N, 9.24

Found (%): C, 57.81; H, 5.79; N, 9.53

[0061]

Example 6

1-{3-[(6-Bromo-2-naphthyl)sulfonyl]propanoyl}-4-(4-methyl-

1H-imidazol-1-yl)piperidine

From tert-butyl 4-(4-methyl-1H-imidazol-1-y)piperidine-1-carboxylate (JP-A 7-501556) (0.39 g) and 3-[(6-bromo-2-naphthyl)sulfonyl]propionic acid (0.45 g), the title compound (0.49 g, 75%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.68-1.86 (2H, m), 2.12-2.27 (2H, m), 2.21 (3H, d, J = 0.6), 2.60-2.73 (1H, m), 2.89-2.96 (2H, m), 3.10-3.24 (1H, m), 3.53-3.61 (2H, m), 3.96-4.10 (2H, m), 4.65-4.71 (1H, m), 6.63 (1H, s), 7.41 (1H, d, J = 1.4), 7.73 (1H, dd, J = 8.8 and 2.0), 7.84-7.93 (3H, m), 8.13 (1H, d, J = 1.6), 8.48 (1H, s).

Elemental analysis for $C_{22}H_{24}BrN_3O_3S \cdot H_2O$

Calculated (%): C, 51.97; H, 5.15; N, 8.26

Found (%): C, 52.03; H, 4.99; N, 8.39

[0062]

Example 7

7a) Tert-butyl 4-(2,4-dimethyl-1H-imidazol-1-yl)piperidine-1-carboxylate

A suspension of 2,4-dimethylimidazole (5.16 g), tert-butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (10 g) and potassium carbonate (4.95 g) in DMF (80 mL) was stirred at 100°C for 72 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water and ethyl acetate. An organic layer was

separated, washed with saturated sodium hydrogencarbonate, and then dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. The residue was purified with a silica gel column (dichloromethane/methanol/aqueous ammonia = 100/3.5/0.5 to 100/10/1) to obtain the title compound (0.58 g, 6%) as a yellow oil.

NMR (300 MHz, $CDCl_3$) δ: 1.43 (9H, s), 1.66-1.92 (3H, m), 2.16 (3H, s), 2.37 (3H, s), 2.77-2.85 (2H, m), 3.79-3.91 (2H, m), 4.26 (2H, m), 6.55 (1H, s).

7b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2,4-dimethyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2,4-dimethyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.28 g) obtained in Example 7a), the title compound (0.21 g, 46%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.65-1.79 (2H, m), 1.93-2.05 (2H, m), 2.16 (3H, d, J = 0.9), 2.37 (3H, s), 2.58-2.67 (1H, m), 2.90-2.97 (2H, m), 3.13-3.22 (1H, m), 3.54-3.61 (2H, m), 3.95-4.04 (2H, m), 4.71-4.75 (1H, m), 6.50 (1H, d, J = 1.2), 7.60 (1H, dd, J = 8.7 and 1.8), 7.91-7.97 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S \cdot H_2O$

Calculated (%): C, 57.79; H, 5.90; N, 8.79

Found (%): C, 57.84; H, 5.90; N, 8.68

[0063]

Example 8

1-{3-[(6-Bromo-2-naphthyl)sulfonyl]propanoyl}-4-(2,4-dimethyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2,4-dimethyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.29 g) obtained in Example 7a) and 3-[(6-bromo-2-naphthyl)sulfonyl]propionic acid (0.36 g), the title compound (70 mg, 14%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.65-1.79 (2H, m), 1.94-2.00 (2H, m), 2.16 (3H, d, J = 0.6), 2.37 (3H, s), 2.59-2.68 (1H, m), 2.90-2.97 (2H, m), 3.13-3.22 (1H, m), 3.54-3.61 (2H, m), 3.95-4.03 (2H, m), 4.71-4.76 (1H, m), 6.50 (1H, s), 7.74 (1H, dd, J = 8.8 and 2.0), 7.85-7.98 (3H, m), 8.14 (1H, d, J = 2.1), 8.48 (1H, s).

Elemental analysis for $C_{23}H_{26}BrN_3O_3S \cdot H_2O$

Calculated (%): C, 52.87; H, 5.40; N, 8.04

Found (%): C, 52.66; H, 5.23; N, 8.03

[0064]

Example 9

9a) Tert-butyl 4-(2-ethyl-1H-imidazol-1-yl)piperidine-1-carboxylate

From 2-ethylimidazole (4.13 g), the title compound (1.10 g, 11%) was obtained as a yellow oil in a similar manner to Example 7a).

NMR (300 MHz, $CDCl_3$) δ: 1.31-1.39 (3H, m), 1.49 (9H, s), 1.70-1.95 (4H, m), 2.67-2.87 (4H, m), 3.96-4.01 (1H, m), 4.29-4.33 (2H, m), 6.86 (1H, d, J = 1.5), 6.97 (1H, d, J = 1.5)

9b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2-ethyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.28 g) obtained in Example 9a), the title compound (0.45 g, 98%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.36 (3H, t, J = 7.4), 1.65-1.86 (2H, m), 1.96-2.05 (2H, m), 2.61-2.68 (1H, m), 2.71 (2H, q, J = 7.5), 2.91-2.98 (2H, m), 3.16-3.24 (1H, m), 3.54-3.62 (2H, m), 4.01-4.13 (2H, m), 4.73-4.77 (1H, m), 6.81 (1H, d, J = 1.8), 6.98 (1H, d, J = 1.5), 7.60 (1H, dd, J = 8.7 and 1.8), 7.94-7.97 (4H, m), 8.49 (1H, d, J = 0.6).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 58.90; H, 5.80; N, 8.96

Found (%): C, 58.72; H, 6.05; N, 9.08

[0065]

Example 10

10a) Tert-butyl 4-(2-isopropyl-1H-imidazol-1-yl)piperidine-1-carboxylate

From 2-isopropylimidazole (4.73 g), the tile compound (0.40 g, 4%) was obtained as a yellow oil in a similar

manner to Example 7a).

NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, s), 1.36 (3H, s), 1.49 (9H, s), 1.76-1.95 (4H, m), 2.78-2.88 (2H, m), 2.95-3.08 (1H, m), 4.06-4.14 (1H, m), 4.29-4.34 (2H, m), 6.84 (1H, d, J = 1.6), 6.98 (1H, d, J = 1.2).

10b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-isopropyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2-isopropyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.29 g) obtained in Example 10a), the title compound (0.36 g, 76%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.32-1.36 (6H, m), 1.70-1.86 (2H, m), 1.96-2.05 (2H, m), 2.61-2.69 (1H, m), 2.91-3.05 (3H, m), 3.16-3.25 (1H, m), 3.55-3.62 (2H, m), 4.01-4.18 (2H, m), 4.73-4.78 (1H, m), 6.78 (1H, d, J = 1.5), 6.98 (1H, d, J = 1.2), 7.60 (1H, dd, J = 8.9 and 2.0), 7.94-7.97 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{24}H_{28}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 59.68; H, 6.05; N, 8.70

Found (%): C, 59.51; H, 6.22; N, 8.53

[0066]

Example 11

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-propyl-1H-imidazol-1-yl)piperidine

11a) Tert-butyl 4-(2-propyl-1H-imidazol-1-yl)piperidine-1-

carboxylate

From 2-propylimidazole (4.73 g, 43 mmol), the title compound (0.28 g, 3%) was obtained as a yellow oil in a similar manner to Example 7a).

NMR (300 MHz, $CDCl_3$) δ: 0.98-1.04 (3H, m), 1.49 (9H, s), 1.71-1.94 (6H, m), 2.59-2.69 (2H, m), 2.79-2.87 (2H, m), 3.96-4.04 (1H, m), 4.28-4.33 (2H, m), 6.85 (1H, d, J = 1.2), 6.97 (1H, d, J = 1.5).

11b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-propyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2-propyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.28 g) obtained in Example 11a), the title compound (0.30 g, 66%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.02 (3H, t, J = 7.5), 1.68-2.05 (6H, m), 2.62-2.69 (3H, m), 2.90-2.99 (2H, m), 3.14-3.26 (1H, m), 3.54-3.63 (2H, m), 4.01-4.14 (2H, m), 4.71-4.78 (1H, m), 6.80 (1H, d, J = 1.4), 6.97 (1H, d, J = 1.0), 7.60 (1H, dd, J = 8.8 and 1.8), 7.89-7.98 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{24}H_{28}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 59.68; H, 6.05; N, 8.70

Found (%): C, 59.74; H, 6.30; N, 8.62

[0067]

Example 12

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-butyl-

1H-imidazol-1-yl)piperidine

12a) Tert-butyl 4-(2-butyl-1H-imidazol-1-yl)piperidine-1-carboxylate

From 2-butylimidazole (6.66 g), the title compound (0.33 g, 3%) was obtained as a yellow oil in a similar manner to Example 7a).

NMR (300 MHz, $CDCl_3$) δ: 0.98-1.94 (11H, s), 1.49 (9H, s), 2.59-2.69 (2H, m), 2.79-2.87 (2H, m), 3.96-4.04 (1H, m), 4.28-4.33 (2H, m), 6.85 (1H, d, J = 1.2), 6.97 (1H, d, J = 1.5).

12b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-butyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(2-butyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.31 g) obtained in Example 12a), the title compound (0.41 g, 85%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 0.96 (3H, t, J = 7.3), 1.33-1.52 (2H, m), 1.67-2.05 (6H, m), 2.50-2.90 (3H, m), 2.90-2.99 (2H, m), 3.08-3.27 (1H, m), 3.52-3.63 (2H, m), 4.01-4.14 (2H, m), 4.71-4.79 (1H, m), 6.80 (1H, d, J = 1.4), 6.97 (1H, d, J = 1.2), 7.58-7.63 (1H, m), 7.89-7.98 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{25}H_{30}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 60.41; H, 6.29; N, 8.45

Found (%): C, 60.33; H, 6.33; N, 8.40

[0068]

Example 13

[1-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1H-imidazol-2-yl]methanol

13a) Tert-butyl 4-(2-formyl-1H-imidazol-1-yl)piperidine-1-carboxylate

From 2-formylimidazole (2.06 g), the title compound (1.88 g, 38%) was obtained as colorless powder in a similar manner to Example 7a).

NMR (200 MHz, $CDCl_3$+CD_3OD) δ: 1.48 (9H, s), 1.71-1.79 (2H, m), 2.10 (2H, m), 2.84-2.97 (2H, m), 4.26-4.32 (2H, m), 5.10-5.30 (1H, m), 7.32-7.36 (2H, m), 9.82 (1H, d, J = 0.8).

13b) Tert-butyl 4-(2-hydroxymethyl-1H-imidazol-1-yl)piperidine-1-carboxylate

Tert-butyl 4-(2-formyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.48 g) obtained in Example 13a) was dissolved in methanol (20 mL), and sodium borohydride (0.14 g) was added thereto. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with an aqueous saturated sodium bicarbonate solution and ethyl acetate. An organic layer was separated, washed with an aqueous saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound (0.40 g, 83%) as colorless

powder.

NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.68-1.85 (2H, m), 2.00-2.06 (2H, m), 2.79-2.92 (2H, m), 4.26-4.40 (3H, m), 4.68 (2H, s), 6.91 (2H, s).

13c) [1-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1H-imidazol-2-yl]methanol

From tert-butyl 4-(2-hydroxymethyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.38 g) obtained in Example 13b), the title compound (0.26 g, 42%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$+CD_3OD) δ: 1.69-1.83 (2H, m), 2.05-2.18 (2H, m), 2.37-2.58 (2H, m), 2.63-2.75 (1H, m), 2.87-2.99 (2H, m), 3.18-3.30 (1H, m), 3.53-3.64 (2H, m), 3.98-4.05 (1H, m), 4.40-4.52 (1H, m), 4.68-4.76 (1H, m), 6.92 (2H, d, J = 4.8), 7.61 (1H, dd, J = 8.8 and 1.8), 7.90-8.00 (4H, m), 8.50 (1H, s).

Elemental analysis for $C_{22}H_{24}ClN_3O_4S \cdot 0.4H_2O$

Calculated (%): C, 56.32; H, 5.33; N, 8.96

Found (%): C, 56.49; H, 5.08; N, 8.68

[0069]

Example 14

1-[1-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1H-imidazol-2-yl]ethanol

Tert-butyl 4-(2-formyl-1-imidazol-1-yl)piperidine-1-carbopxylate (0.48 g) obtained in Example 13a) was

dissolved in THF (10 mL), and methylmagnesium bromide (3M diethyl ether solution; 1.0 mL) was added while cooling to 0°C thereto. The mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with an aqueous saturated ammonium chloride solution. An organic layer was separated, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resulting residue was dissolved in a 4N solution of hydrogen chloride in ethyl acetate (5 mL). The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and then subjected to azeotropic distillation with ethanol to remove water. The residue was dissolved in acetonitrile (15 mL) together with DBU (0.26 g) and triethylamine (0.26 g). This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.25 g), HOBt (0.20 g) and WSC (0.24 g) in acetonitrile (15 mL), and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure and diluted with ethyl acetate and an aqueous potassium carbonate solution. An organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate) to obtain the title compound (50 mg, 10%) as pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.67-2.20 (7H, m), 2.59-2.72 (1H, m), 2.88-2.99 (2H, m), 3.14-3.27 (1H, m), 3.40-3.70 (2H, m), 3.98-4.07 (1H, m), 4.38-4.60 (1H, m), 4.72-4.78 (1H, m), 4.88-4.98 (1H, m), 6.88 (1H, s), 6.98 (1H, d, J = 0.8), 7.60 (1H, dd, J = 8.8 and 1.8), 7.89-7.98 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{23}H_{26}ClN_3O_4S \cdot 0.5H_2O$

Calculated (%): C, 56.96; H, 5.61; N, 8.66

Found (%): C, 57.18; H, 5.76; N, 8.47

[0070]

Example 15

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(4,5-dimethy-1H-imidazol-1-yl)piperidine

15a) Tert-butyl 4-(4,5-dimethyl-1H-imidazol-1-yl)piperidine-1-carboxylate

From 4,5-dimethylimidazole (JP-A 60-56961) (5.00 g), the title compound (0.27 g, 3%) was obtained as a yellow oil in a similar manner to Example 7a).

NMR (200 MHz, $CDCl_3$) δ: 1.48 (9H, s), 1.74-1.89 (2H, m), 1.96-2.02 (2H, m), 2.14 (3H, s), 2.15 (3H, s), 2.76-2.89 (2H, m), 3.75-3.89 (1H, m), 4.26-4.33 (2H, m), 7.38 (1H, s).

15b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(4,5-dimethyl-1H-imidazol-1-yl)piperidine

From tert-butyl 4-(4,5-dimethyl-1H-imidazol-1-yl)piperidine-1-carboxylate (0.27 g) obtained in Example

15a), the tile compound (0.14 g, 30%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.67-1.85 (2H, m), 2.00-2.19 (2H, m), 2.15 (6H, s), 2.58-2.70 (1H, m), 2.90-2.98 (2H, m), 3.13-3.25 (1H, m), 3.53-3.61 (2H, m), 3.86-4.07 (2H, m), 4.71-4.76 (1H, m), 7.35 (1H, s), 7.61 (1H, dd, J = 1.8 and 8.8), 7.93-7.98 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S \cdot H_2O$

Calculated (%): C, 57.79; H, 5.90; N, 8.79

Found (%): C, 57.95; H, 5.77; N, 8.72

[0071]

Example 16

1-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-2-methyl-1H-benzimidazole

16a) Tert-butyl 4-(2-methyl-1H-benzimidazol-1-yl)piperidine-1-carboxylate

Sodium hydride (1.50 g) was added to a solution of 2-methylbenzimidazole (5.20 g) in DMF (80 mL) at 0°C, and the mixture was stirred at 0°C for 30 minutes. Tert-butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (10 g) was added to the mixture, which was stirred at 100°C for 48 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with an aqueous sodium hydrogencarbonate solution and ethyl acetate. An organic layer was separated, washed with an aqueous

saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. The residue was purified with a silica gel column (ethyl acetate/hexane = 1/1 to 3/1) to obtain the title compound (0.77 g, 7%) as a colorless solid.
NMR (300 MHz, $CDCl_3$) δ: 1.53 (9H, s), 1.87-1.91 (2H, m), 2.37-2.50 (2H, m), 2.65 (3H, s), 2.84-2.94 (2H, m), 4.27-4.40 (3H, m), 7.18-7.22 (2H, m), 7.42-7.45 (1H, m), 7.68-7.71 (1H, m).

16b) 1-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-2-methyl-1H-benzimidazole

From tert-butyl 4-(2-methyl-1H-benzimidazol-1-yl)piperidine-1-carboxylate (0.18 g, 0.6 mmol) obtained in Example 16a), the title compound (0.24 g, 48%) was obtained as colorless powder in a similar manner to Example 1.
NMR (200 MHz, $CDCl_3$) δ: 1.90-2.05 (2H, m), 2.38-2.52 (2H, m), 2.65 (3H, s), 2.65-2.77 (1H, m), 2.95-3.06 (2H, m), 3.20-3.32 (1H, m), 3.57-3.67 (2H, m), 4.07-4.18 (1H, m), 4.34-4.46 (1H, m), 4.83-4.89 (1H, m), 7.17-7.23 (2H, m), 7.39-7.43 (1H, m), 7.61 (1H, dd, J = 8.9 and 1.9), 7.67-7.71 (1H, m), 7.95-7.99 (4H, m), 8.52 (1H, s).
Elemental analysis for $C_{26}H_{26}ClN_3O_3S \cdot H_2O$
Calculated (%): C, 60.75; H, 5.49; N, 8.17
Found (%): C, 60.88; H, 5.64; N, 7.99

[0072]

Example 17

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-4-yl)-4-piperidinol

From tert-butyl 4-hydroxy-4-(1H-imidazol-4-yl)piperidine-1-carboxylate (Tetrahedron, 51, 13447 (1995))(0.27 g), the title compound(0.08 g, 18%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.81-1.96 (4H, m), 2.86-2.93 (3H, m), 3.12-3.26 (2H, m), 3.53-3.63 (4H, m), 4.21-4.28 (1H, m), 6.87 (1H, d, J = 1.2), 7.56-7.61 (2H, m), 7.88-7.97 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{21}H_{22}ClN_3O_4S \cdot 0.5H_2O$

Calculated (%): C, 55.20; H, 5.07; N, 9.20

Found (%): C, 55.45; H, 5.11; N, 9.30

[0073]

Example 18

1-{3-[(6-Bromo-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-4-yl)-4-piperidinol

From tert-butyl 4-hydroxy-4-(1H-imidazol-4-yl)piperidine-1-carboxylate (0.27 g) and 3-[(6-bromo-2-naphthyl)sulfonyl]propionic acid (0.34 g), the title compound (0.14 g, 28%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.81-1.95 (4H, m), 2.86-2.93 (3H,

m), 3.10-3.23 (2H, m), 3.47-3.63 (4H, m), 4.22-4.29 (1H, m), 6.87 (1H, d, J = 1.2), 7.61 (1H, d, J = 1.0), 7.71 (1H, dd, J = 2.0 and 8.6), 7.83-7.93 (3H, m), 8.12 (1H, s), 8.47 (1H, s).

Elemental analysis for $C_{21}H_{22}BrN_3O_4S \cdot 0.5H_2O$

Calculated (%): C, 50.30; H, 4.62; N, 8.38

Found (%): C, 50.46; H, 4.86; N, 8.54

[0074]

Example 19

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-4-yl)-1,2,3,6-tetrahydropyridine

4-(1H-Imidazol-4-yl)-1,2,3,4-tetrahydropyridine dihydrochloride (Tetrahedron, 51, 13447 (1995)) (0.13 g), DBU (0.15 g) and triethylamine (0.15 g) in acetonitrile (5 mL) were added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.15 g), HOBt (0.12 g) and WSC (0.14 g) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated under reduced pressure and diluted with ethyl acetate and an aqueous potassium carbonate solution. An organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate to ethyl acetate/methanol = 20/1) to obtain the title compound (0.11 g, 49%) as

colorless powder.

NMR (300 MHz, $CDCl_3$) δ: 2.34 (1H, m), 2.53 (1H, m), 2.87 (1H, t, J = 7.7), 2.94 (1H, t, J = 7.8), 3.58-3.71 (4H, m), 4.11-4.13 (2H, m), 6.24 (1H, d, J = 16.5), 6.96 (1H, d, J = 6.9), 7.54-7.58 (1H, m), 7.63 (1H, s), 7.91-7.94 (4H, m), 8.47 (1H, s).

Elemental analysis for $C_{21}H_{20}ClN_3O_3S \cdot 0.6H_2O$

Calculated (%): C, 57.23; H, 4.85; N, 9.53

Found (%): C, 57.04; H, 4.77; N, 9.35

[0075]

Example 20

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-4-yl)piperidine

From 4-(1H-imidazol-4-yl)piperidine dihydrochloride (Tetrahedron, 51, 13447 (1995)) (0.46 g), the title compound (0.43 g, 50%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$+CD_3OD) δ: 1.40-1.60 (2H, m), 1.95-2.11 (2H, m), 2.66-2.91 (5H, m), 3.13-3.20 (1H, m), 3.54-3.61 (2H, m), 3.86-3.90 (1H, m), 4.47-4.51 (1H, m), 6.70 (1H, s), 7.53 (1H, d, J = 1.2), 7.59 (1H, dd, J = 8.4 and 2.4), 7.93-7.98 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{21}H_{22}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 57.20; H, 5.26; N, 9.53

Found (%): C, 57.48; H, 5.05; N, 9.44

[0076]

Example 21

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-methyl-1H-imidazol-5-yl)piperidine

21a) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-trityl-1H-imidazol-4-yl)piperidine

1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-4-yl)piperidine (0.35 g) obtained in Example 20 and triethylamine (0.10 g) were dissolved in DMF (10 mL), triphenylchloromethane (0.25 g) was added at 0°C thereto. The mixture was stirred at 0°C for 1 hour and then at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with an aqueous saturated sodium bicarbonate solution and ethyl acetate. An organic layer was separated, washed with an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate) to obtain the title compound (0.54 g, quantitative) as colorless powder.
NMR (200 MHz, $CDCl_3$) δ: 1.40-1.50 (2H, m), 1.92-2.10 (2H, m), 2.58-2.87 (4H, m), 3.04-3.17 (1H, m), 3.51-3.59 (2H, m), 3.78-3.84 (1H, m), 4.41-4.47 (1H, m), 6.49 (1H, s), 7.09-7.35 (16H, m), 7.57 (1H, dd, J = 8.8 and 1.8), 7.92-8.02 (4H, m), 8.46 (1H, s).

21b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-methyl-1H-imidazol-5-yl)piperidine

1-{3-[(6-Chloro-2-naphtyl)sulfonyl]propanoyl}-4-(1-trityl-1H-imidazol-4-yl)piperidine (0.54 g) obtained in Example 21a) and methyl iodide (0.10 mL) were dissolved in DMF (5 mL), and the mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in acetic acid (5 mL), water (5 mL) and methanol (2 mL). The solution was stirred at 95°C for 2 hours. The reaction mixture was concentrated under reduced pressure. After the residue was basified by addition of an aqueous saturated sodium bicarbonate solution, ethyl acetate was added thereto. An organic layer was separated, washed with an aqueous saturated bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate to ethyl acetate/methanol = 10/1) to obtain the title compound (0.27 g, 76%) as colorless powder.

NMR (200 MHz, $CDCl_3$) δ: 1.43-1.70 (2H, m), 1.88-2.04 (2H, m), 2.60-2.78 (2H, m), 2.87-2.95 (2H, m), 3.09-3.22 (1H, m), 3.53-3.61 (2H, m), 3.60 (3H, s), 3.91-3.98 (1H, m), 4.55-4.62 (1H, m), 6.76 (1H, s), 7.38 (1H, s), 7.59 (1H, dd, J = 8.8 and 1.8), 7.93-7.97 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{22}H_{24}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 58.08; H, 5.54; N, 9.24

Found (%): C, 57.79; H, 5.74; N, 9.26

[0077]

Example 22

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-methyl-1H-imidazol-4-yl)piperidine

From 4-(2-methyl-1H-imidazol-4-yl)piperidine dihydrochloride (Farmaco, 47, 1343 (1992))(1.00 g), the title compound (1.70 g, 91%) was obtained as colorless powder in a similar manner to Example 19.

NMR (200 MHz, $CDCl_3$) δ: 1.41-1.60 (2H, m), 1.93-2.10 (2H, m), 2.39 (3H, s), 2.59-2.71 (2H, m), 2.83-2.91 (2H, m), 3.07-3.21 (1H, m), 3.53-3.60 (2H, m), 3.83-3.90 (1H, m), 4.47-4.54 (1H, m), 6.56 (1H, s), 7.58 (1H, dd, J = 9.0 and 2.0), 7.88-7.97 (4H, m), 8.48 (1H, br).

Elemental analysis for $C_{22}H_{24}ClN_3O_3S \cdot 0.2H_2O$

Calculated (%): C, 58.78; H, 5.47; N, 9.35

Found (%): C, 58.68; H, 5.25; N, 9.29

[0078]

Example 23

1-{3-[(6-Chloro-2-naphthyl)sulufonyl]propanoyl}-4-(2-methyl-1-trityl-1H-imidazol-4-yl)piperidine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-methyl-1H-imidazol-4-yl)piperidine (1.30 g) obtained in Example 22, the title compound (1.20 g, 60%) was obtained

as colorless powder in a similar manner to Example 21a).
NMR (300 MHz, $CDCl_3$) δ: 1.33-1.59 (2H, m), 1.90-2.06 (2H, m), 2.57-2.74 (2H, m), 2.82-2.89 (2H, m), 3.05-3.13 (1H, m), 3.52-3.57 (2H, m), 3.80-3.84 (1H, m), 4.45-4.49 (1H, m), 6.34 (1H, s), 7.09-7.12 (5H, m), 7.30-7.35 (10H, m), 7.58 (1H, dd, J = 8.7 and 1.8), 7.91-7.96 (4H, m), 8.47 (1H, s).

[0079]

Example 24

1-{3-[(6-Chloro-2-naphthyl)sulufonyl]propanoyl}-4-(1,2-dimethyl-1H-imidazol-5-yl)piperidine

From 1-{3-[(6-chloro-2-naphthyl)sulufonyl]propanoyl}-4-(2-methyl-1-trityl-1H-imidazol-4-yl)piperidine (0.28 g) obtained in Example 23, the title compound (0.09 g, 48%) was obtained as colorless powder in a similar manner to Example 21b).
NMR (200 MHz, $CDCl_3$) δ: 1.40-1.56 (2H, m), 1.87-2.00 (2H, m), 2.36 (3H, s), 2.60-2.71 (2H, m), 2.87-2.95 (2H, m), 3.09-3.21 (1H, m), 3.45 (3H, s), 3.53-3.61 (2H, m), 3.90-3.96 (1H, m), 4.54-4.60 (1H, m), 6.60 (1H, s), 7.60 (1H, dd, J = 8.8 and 1.8), 7.93-7.97 (4H, m), 8.49 (1H, s).
Elemental analysis for $C_{23}H_{26}ClN_3O_3S \cdot H_2O$
Calculated (%): C, 57.79; H, 5.90; N, 8.79
Found (%): C, 57.75; H, 5.87; N, 8.50

[0080]

Example 25

2-[5-(1-{3-[(6-Chloro-2-naphthyl)sulufonyl]propanoyl}-4-piperidinyl)-2-methyl-1H-imidazol-1-yl]acetamide

From 1-{3-[(6-chloro-2-naphthyl)sulufonyl]propanoyl}-4-(2-methyl-1-trityl-1H-imidazol-4-yl)piperidine (0.69 g) obtained in Example 23 and iodoacetamide (0.28 g), the title compound (0.10 g, 20%) was obtained as colorless powder in a similar manner to Example 21b).

NMR (300 MHz, $CDCl_3$) δ: 1.38-1.58 (2H, m), 1.94-2.10 (2H, m), 2.35 (3H, s), 2.60-2.77 (2H, m), 2.85-2.91 (2H, m), 3.08-3.18 (1H, m), 3.54-3.59 (2H, m), 3.86-3.90 (1H, m), 4.50 (2H, s), 4.50-4.56 (1H, m), 5.37 (1H, br), 5.55 (1H, br), 6.54 (1H, s), 7.59 (1H, dd, J = 9.0 and 2.1), 7.90-7.97 (4H, m), 8.48 (1H, d, J = 0.9).

Elemental analysis for $C_{24}H_{27}ClN_4O_4S \cdot 0.8H_2O$

Calculated (%): C, 55.71; H, 5.57; N, 10.83

Found (%): C, 55.87; H, 5.57; N, 10.90

[0081]

Example 26

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1H-imidazol-4-yl)piperidine

26a) 4-(2-Ethyl-1H-imidazol-4-yl)pyridine

2,2-Diethoxy-2-(4-pyridinyl)ethylamine (Org. Synth., 64, 19 (1985)) (1.24 g) and ethyl propaneimidate (1.38 g) were dissolved in ethanol (30 mL), and the mixture was heated to reflux for 24 hours. The reaction mixture was

concentrated under reduced pressure. After the residue was basified by addition of an aqueous potassium carbonate solution, ethyl acetate was added thereto. An organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate to ethyl acetate/methanol = 10/1) to obtain the title compound (0.65 g, 38%) as a yellow solid.

NMR (300 MHz, $CDCl_3$) δ: 1.36 (3H, t, J = 7.7), 2.83 (2H, q, J = 7.7), 7.42 (1H, s), 7.63 (2H, d, J = 5.1), 8.54 (2H, dd, J = 4.7 and 1.7), 10.50 (1H, br).

26b) 4-(2-Ethyl-1H-imidazol-4-yl)piperidine dihydrochloride

4-(2-Ethyl-1H-imidazol-4-yl)pyridine (0.60 g, 3.2 mmol) obtained in Example 26a) and 5% rhodium carbon (50% hydrous, 0.10 g) were added to 1N hydrochloric acid (40 mL), and the mixture was stirred at room temperature for 6 hours under 5 atm hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (0.70 g, 81%) as colorless powder.

NMR (200 MHz, DMSO-d_6) δ: 1.29 (3H, t, J = 7.6), 1.69-1.86 (2H, m), 2.14-2.20 (2H, m), 2.90 (2H, q, J = 7.6), 2.90-3.55 (5H, m), 7.37 (1H, d, J = 0.8), 9.06 (2H, br).

26c) 1-{3-[(6-Chloro-2-naphthyl)sulufonyl]propanoyl}-4-(2-ehtyl-1H-imidazol-4-yl)piperidine

From 4-(2-ethyl-1H-imidazol-4-yl)piperidine dihydrochloride (0.65 g) obtained in Example 26b), the title compound (0.30 g, 25%) was obtained as colorless powder in a similar manner to Example 19.

NMR (300 MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.8), 1.40-1.55 (2H, m), 1.95-2.10 (2H, m), 2.61-2.70 (2H, m), 2.73 (2H, q, J = 7.8), 2.85-2.90 (2H, m), 3.08-3.18 (1H, m), 3.54-3.60 (2H, m), 3.84-3.88 (1H, m), 4.49-4.53 (1H, m), 6.58 (1H, s), 7.58 (1H, dd, J = 8.7 and 1.8), 7.92-7.96 (4H, m), 8.48 (1H, s), 8.62 (1H, br).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S \cdot 0.2H_2O$

Calculated (%): C, 59.59; H, 5.74; N, 9.06

Found (%): C, 59.50; H, 5.50; N, 8.98

[0082]

Example 27

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1-trityl-1H-imidazol-4-yl)piperidine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1H-imdazol-4-yl)piperidine (0.25 g) obtained in Example 26c), the title compound (0.30 g, 79%) was obtained as colorless powder in a similar manner to Example 21a).

NMR (200 MHz, $CDCl_3$) δ: 0.71 (3H, t, J = 7.5), 1.30-1.46 (2H, m), 1.91 (2H, q, J = 7.6), 1.93-2.10 (2H, m), 2.53-2.89 (4H, m), 3.01-3.18 (1H, m), 3.50-3.58 (2H, m), 3.78-3.84 (1H, m), 4.43-4.49 (1H, m), 6.28 (1H, s), 7.08-7.13

(5H, m), 7.27-7.34 (10H, m), 7.58 (1H, dd, J = 8.8 and 1.8), 7.92-8.02 (4H, m), 8.47 (1H, s).

[0083]

Example 28

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1-methyl-1H-imidazol-5-yl)piperidine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2-ethyl-1-trityl-1H-imidazol-4-yl)piperidine (0.30 g) obtained in Example 27, the title compound (0.09 g, 45%) was obtained as colorless powder in a similar manner to Example 21b).

NMR (200 MHz, $CDCl_3$) δ: 1.33 (3H, t, J = 7.0), 1.48-1.63 (2H, m), 1.88-2.05 (2H, m), 2.61-2.73 (4H, m), 2.87-2.95 (2H, m), 3.08-3.22 (1H, m), 3.46 (3H, s), 3.53-3.61 (2H, m), 3.90-3.96 (1H, m), 4.54-4.61 (1H, m), 6.64 (1H, s), 7.60 (1H, dd, J = 9.0 and 2.0), 7.93-7.97 (4H, m), 8.48 (1H, d, J = 1.2).

Elemental analysis for $C_{24}H_{28}ClN_3O_3S \cdot H_2O$

Calculated (%): C, 58.59; H, 6.15; N, 8.54

Found (%): C, 58.72; H, 6.19; N, 8.38

[0084]

Example 29

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2,4-dimethyl-1H-imidazol-5-yl)piperidine

29a) 4-(2,4-Dimethyl-1H-imidazol-5-yl)pyridine

Sodium hydride (60%; 0.67 g) was added to a solution of 2,4-dimethyl-5-iodoimidazole (Tetrahedron, 54, 3235 (1998)) (3.40 g) in DMF (20 mL) at 0°C and the mixture was stirred at 0°C for 30 minutes. Then, benzyl bromide (2.0 mL) was added to the mixture and stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with water and ethyl acetate. An organic layer was separated, washed with an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a silica gel column (ethyl acetate/hexane = 1/1 to 3/1) to obtain a benzyl compound (4.30 g, 90%) as a colorless oil.

The resulting benzyl compound (1.60 g) together with 4-pyridinylboronic acid (0.63 g), tetrakistriphenylphosphine palladium (0.59 g) and potassium t-butoxide (4.60 g) was added to a dimethoxyethane (70 mL)-water (25 mL) mixture, and the mixture was heated to reflux for 40 hours. The reaction mixture was diluted with an aqueous saturated sodium bicarbonate solution and ethyl acetate. An organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate/hexane = 2/1 to ethyl acetate) to

obtain a pyridine compound (0.64 g, 47%) as a yellow oil.

To a solution of the pyridine compound (0.60 g) in methanol (100 mL) were added 10% Palladium carbon (50%; 0.60 g) and then ammonium formate (3.00 g), and the mixture was heated to reflux for 2 hours. The reaction solution was cooled to room temperature, ammonium formate (4.00 g) was added, and the mixture was further heated to reflux for 15 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate to ethyl acetate/methanol = 10/1) to obtain the title compound (0.10 g, 25%) as colorless powder.

NMR (300 MHz, $CDCl_3$) δ: 2.45 (3H, s), 2.48 (3H, s), 7.57 (2H, br), 8.57 (2H, dd, J = 6.3 and 1.7), 8.88 (1H, br).

29b) 4-(2,4-Dimethyl-1H-imidazol-5-yl)piperidine dihydrochloride

From 4-(2,4-dimethyl-1H-imidazol-5-yl)pyridine (0.10 g) obtained in Example 29a), the title compound (0.15 g, quantitative) was obtained as colorless powder in a similar manner to Example 26b).

NMR (200 MHz, CD_3OD) δ: 2.00-2.08 (4H, m), 2.29 (3H, s), 2.57 (3H, s), 3.08-3.23 (3H, m), 3.49-3.55 (2H, m).

29c) 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-(2,4-dimethyl-1H-imidazol-5-yl)piperidine

From 4-(2,4-Dimethyl-1H-imidazol-5-yl)piperidine

dihydrochloride (0.15 g) obtained in Example 29b), the title compound (0.16 g, 60%) was obtained as colorless powder in a similar manner to Example 19.

NMR (200 MHz, $CDCl_3$) δ: 1.62-1.80 (4H, m), 2.15 (3H, s), 2.32 (3H, s), 2.52-2.80 (2H, m), 2.84-2.92 (2H, m), 3.03-3.18 (1H, m), 3.53-3.60 (2H, m), 3.89-3.95 (1H, m), 4.57-4.63 (1H, m), 7.59 (1H, dd, J = 9.0 and 2.0), 7.94-7.98 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S$

Calculated (%): C, 60.05; H, 5.70; N, 9.14

Found (%): C, 59.82; H, 5.73; N, 9.27

[0085]

Example 30

5-Chloro-1H-indol-2-yl 3-[4-(2-methyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropyl sulfonate

30a) Tert-butyl 5-chloro-2-({3-[4-(2-methyl-1H-imidazol-4-yl)-1-piperidinyl]-3-oxopropyl}sulfonyl)-1H-indole-1-carboxylate

From 4-(2-methyl-1H-imidazol-4-yl)piperidine dihydrochloride (0.71 g) and 3-{[1-(tert-butoxycarbonyl)-5-chloro-1H-indol-2-yl]sulfonyl}propionic acid (1.16 g), the title compound (0.70 g, 44%) was obtained as colorless powder in a similar manner to Example 19.

NMR (200 MHz, $CDCl_3$) δ: 1.46-2.10 (4H, m), 1.73 (9H, s), 2.39 (3H, s), 2.61-2.80 (2H, m), 2.88-2.96 (2H, m), 3.05-

3.20 (1H, m), 3.84-3.91 (1H, m), 4.00-4.10 (2H, m), 4.48-4.56 (1H, m), 6.57 (1H, s), 7.43 (1H, dd, J = 9.4 and 2.2), 7.63 (1H, d, J = 2.0), 8.01 (1H, d, J = 9.2).

30b) 5-Chloro-1H-indol-2-yl 3-[4-(2-methyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropylsulfonate

Tert-butyl 5-chloro-2-({3-[4-(2-methyl-1H-imidazol-4-yl)-1-piperidinyl]-3-oxopropyl}sulfonyl)-1H-indole-1-carboxylate (0.26 g) obtained in Example 30a) was dissolved in concentrated hydrochloric acid (1.5 mL), and the solution was stirred at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure, and the residue was washed with isopropyl alcohol to obtain the title compound (0.20 g, 87%) as brown powder.

NMR (200 MHz, CD_3OD) δ: 1.22-1.63 (2H, m), 1.87-2.06 (2H, m), 2.59 (3H, s), 2.60-2.97 (4H, m), 3.11-3.29 (1H, m), 3.61-3.72 (2H, m), 3.95-4.01 (1H, m), 4.35-4.42 (1H, m), 7.30 (1H, dd, J = 8.8 and 2.2), 7.47 (1H, d, J = 9.0), 7.67 (1H, d, J = 2.2).

Elemental analysis for $C_{20}H_{23}ClN_4O_3S \cdot HCl \cdot 0.8C_3H_8O \cdot H_2O$

Calculated (%): C, 50.06; H, 6.08; N, 10.42

Found (%): C, 49.75; H, 5.97; N, 10.13

[0086]

Example 31

5-Chloro-1H-indol-2-yl 3-[4-(2,4-dimethyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropylsulfone

31a) Tert-butyl 5-chloro-2-((3-[4-(2,4-dimethyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropyl)sulfonyl)-1H-indole-1-carboxylate

From 4-(2,4-dimethyl-1H-imidazol-5-yl)piperidine dihydrochloride (0.21 g) obtained in Example 29b) and 3-{[1-(tert-butoxycarbonyl)-5-chloro-1H-indol-2-yl]sulfonyl}propionic acid (0.32 g), the title compound (0.32 g, 70%) was obtained as colorless powder in a similar manner to Example 19.

NMR (200 MHz, $CDCl_3$) δ: 1.46-1.80 (4H, m), 1.73 (9H, s), 2.17 (3H, s), 2.38 (3H, s), 2.52-3.10 (5H, m), 3.83-3.90 (1H, m), 4.00-4.07 (2H, m), 4.57-4.64 (1H, m), 7.43 (1H, dd, J = 9.2 and 2.2), 7.50 (1H, s), 7.64 (1H, d, J = 2.0), 7.70 (1H, br), 7.99 (1H, d, J = 8.8).

31b) 5-Chloro-1H-indol-2-yl 3-[4-(2,4-dimethyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropylsulfone

Tert-butyl 5-chloro-2-({3-[4-(2,4-dimethyl-1H-imidazol-5-yl)-1-piperidinyl]-3-oxopropyl}sulfonyl)-1H-indole-1-carboxylate (0.32 g) obtained in Example 31a) was dissolved in concentrated hydrochloric acid (3 mL), and the solution was stirred at room temperature for 30 minutes. The reaction solution was neutralized by addition of triethylamine and then concentrated under reduced pressure. The residue was purified with a silica gel column (chloroform/methanol = 20/1 to 5/1) to obtain the title

compound (0.11 g, 42%) as yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.58-1.91 (4H, m), 2.19 (3H, s), 2.33-2.99 (5H, m), 2.46 (3H, s), 3.50-3.96 (3H, m), 4.56-4.63 (1H, m), 7.13 (1H, d, J = 0.8), 7.30 (1H, dd, J = 8.8 and 2.2), 7.46 (1H, d, J = 8.8), 7.68 (1H, d, J = 1.8).

Elemental analysis for $C_{21}H_{25}ClN_4O_3S \cdot 1.1H_2O$

Calculated (%): C, 53.80; H, 5.85; N, 11.95

Found (%): C, 53.62; H, 5.51; N, 11.78

[0087]

Example 32

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-2-yl)-4-piperidinol

From tert-butyl 4-hydroxy-4-(1H-imidazol-2-yl)piperidine-1-carboxylate (JP-A 7-501556) (0.55 g), the title compound (0.11 g, 12%) was obtained as pale brown powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$+CD_3OD) δ: 1.79-2.11(4H, m), 2.87-2.96 (3H, m), 3.13-3.21 (1H, m), 3.50-3.61 (3H, m), 3.66-3.73 (1H, m), 4.11-4.19 (1H, m), 6.95 (1H, d, J = 1.5), 7.59 (1H, dd, J = 2.1 and 8.7), 7.90-7.99 (4H, m), 8.49 (1H, d, J = 1.5).

Elemental analysis for $C_{21}H_{22}ClN_3O_4S$

Calculated (%): C, 56.31; H, 4.95; N, 9.38

Found (%): C, 56.16; H, 4.86; N, 9.43

[0088]

Example 33

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1H-imidazol-2-yl)piperidine

From tert-butyl 4-(1H-imidazol-2-yl)piperidine-1-carboxylate (JP-A 7-501556) (0.26 g), the title compound (0.24 g, 54%) was obtained as colorless powder in a similar manner to Example 1.

NMR (300 MHz, $CDCl_3$) δ: 1.60-1.85 (2H, m), 1.98-2.14 (2H, m), 2.72-3.04 (4H, m), 3.15-3.24 (1H, m), 3.49-3.61 (2H, m), 3.90-3.95 (1H, m), 4.46-4.50 (1H, m), 6.96 (1H, br), 7.00 (1H, br), 7.58 (1H, dd, J = 2.1 and 9.0), 7.90-7.97 (4H, m), 8.48 (1H, d, J = 0.9), 8.88 (1H, br).

Elemental analysis for $C_{21}H_{22}BrN_3O_3S$

Calculated (%): C, 58.39; H, 5.13; N, 9.73

Found (%): C, 58.14; H, 5.13; N, 9.73

[0089]

Example 34

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-methyl-1H-imidazol-2-yl)piperidine

34a) Tert-butyl 4-(1-methyl-1H-imidazol-2-yl)-1-piperidinecarboxylate

Sodium hydride (60%; 40 mg) was added to a solution of tert-butyl 4-(1H-imidazol-2-yl)-1-piperidinecarboxylate (0.25 g) in DMF (3 ml) at 0°C, and the mixture was stirred at 0°C for 30 minutes. Then, methyl iodide (0.06 mL) was

added and the mixture was stirred at 0°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with an aqueous sodium hydrogencarbonate solution and ethyl acetate. An organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. The residue was purified with a silica gel column (chloroform/methanol = 10/1) to obtain the title compound (0.27 g, quantitative) as a pale yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.80-1.91 (4H, m), 2.70-2.96 (3H, m), 3.61 (3H, s), 4.18-4.25 (2H, m), 6.79 (1H, d, J = 1.0), 6.94 (1H, d, J = 1.0).

34b) 1-{3-[(6-Chloro-2-naphtyl)sulfonyl]propanoyl}-4-(1-methyl-1H-imidazol-2-yl)piperidine

From tert-butyl 4-(1-methyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.27 g) obtained in Example 34a), the title compound (0.31 g, 70%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.60-2.00 (4H, m), 2.70-2.94 (4H, m), 3.11-3.26 (1H, m), 3.52-3.61 (2H, m), 3.61 (3H, s), 3.93-4.00 (1H, m), 4.45-4.52 (1H, m), 6.79 (1H, d, J = 1.2), 6.92 (1H, d, J = 1.4), 7.58 (1H, dd, J = 2.0 and 8.8), 7.89-7.98 (4H, m), 8.48 (1H, s), 8.88 (1H, br).

Elemental analysis for $C_{22}H_{24}ClN_3O_3S \cdot 0.5H_2O$

Calculated (%): C, 58.08; H, 5.54; N, 9.24

Found (%): C, 57.98; H, 5.64; N, 9.20

[0090]

Example 35

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(4,5-dimethyl-1H-imidazol-2-yl)piperidine

35a) Tert-butyl 4-hydroxy-4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate

A mixture of 4,5-dimethylimidazole (3.00 g), p-toluenesulfonic acid monohydrate (1.50 g) and triethyl orthoformate (60 mL) was stirred at 130°C for 6 hours. Sodium carbonate (1.50 g) was added, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in THF (50 mL). To the solution was added n-butyllithium (a 1.6 M solution in hexane, 17 mL, 27 mmol) while cooling to -40°C or lower, and then added dropwise was a solution of Boc-piperidone (2.66 g) in THF (20 mL). After completion of addition, the mixture was stirred at -40°C or lower for 2 hours. After the reaction solution was warmed to room temperature, 0.1N hydrochloric acid (40 mL) was added and the mixture was stirred for 15 minutes. Then, ethyl acetate (50 mL) was added and the mixture was stirred for 5 minutes. An organic layer was separated, washed with an aqueous saturated sodium bicarbonate solution and an aqueous saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was

concentrated under reduced pressure. The residue was purified with a silica gel column (chloroform/methanol = 20/1 to 10/1) to obtain the title compound (2.93 g, 21%) as a pale yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.71-1.78 (4H, m), 1.98-2.24 (2H, m), 2.13 (6H, s), 3.17-3.33 (2H, m), 3.89-3.96 (2H, m).

35b) Tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate

Tert-butyl 4-hydroxy-4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (1.96 g) obtained in Example 35a) and diisopropylethylamine (1.68 g) were dissolved in DMF (100 ml). While cooling to 0°C methanesulfonyl chloride (1.52 g) was added, and the mixture was stirred at 0°C for 2 hours. Additional diisopropylethylamine (1.68 g) and methanesulfonyl chloride (1.52 g) were added, and the mixture was stirred at room temperature for 16 hours. The mixture was diluted with water, adjusted to pH 9 by addition of a 1N aqueous sodium hydroxide solution, and then extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the solvent was concentrated under reduced pressure. The residue was purified with a silica gel column (chloroform/methanol = 20/1 to 10/1) to obtain the title compound (1.3 g, 70%) as a pale yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.48 (9H, s), 2.16 (6H, s), 2.59 (2H, br), 3.58 (2H, t, J = 5.7), 4.02-4.06 (2H, m), 6.13 (1H, br).

35c) Tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate

Tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (1.30 g) obtained in Example 35b) and 10% palladium carbon (50% hydrous, 0.20 g) were added to methanol (30 mL), and the mixture was stirred at room temperature for 10 hours under 5 atm hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain the title compound (1.18 g, 90%) as colorless powder.

NMR (200 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.53-1.74 (2H, m), 1.93-1.98 (2H, m), 2.13 (6H, m), 2.75-2.89 (3H, m), 4.14-4.20 (2H, m).

35d) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(4,5-dimethyl-1H-imidazol-2-yl)piperidine

From tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.24 g) obtained in Example 35c), the title compound (53 mg, 13%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.52-2.10 (4H, m), 2.12 (6H, s), 2.63-2.74 (1H, m), 2.83-2.94 (3H, m), 3.08-3.20 (1H, m), 3.52-3.61 (2H, m), 3.87-3.94 (1H, m), 4.48-4.54 (1H, m),

7.58 (1H, dd, J = 2.0 and 8.8), 7.88-7.97 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{23}H_{26}ClN_3O_3S$

Calculated (%): C, 60.05; H, 5.70; N, 9.14

Found (%): C, 59.82; H, 5.67; N, 9.08

[0091]

Example 36

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1,4,5-trimethyl-1H-imidazol-2-yl)piperidine

36a) Tert-butyl 4-(1,4,5-trimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate

From tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.24 g) obtained in Example 35c), the title compound (0.26 g, quantitative) was obtained as a brown oil in a similar manner to Example 34a).

NMR (200 MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.76-1.82 (4H, m), 2.09 (3H, s), 2.13 (3H, s), 2.70-2.90 (3H, m), 3.42 (3H, s), 4.18-4.25 (2H, m).

36b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1,4,5-trimethyl-1H-imidazol-2-yl)piperidine

From tert-butyl 4-(1,4,5-trimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.25 g) obtained in Example 36a), the title compound (0.16 g, 38%) was obtained as colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.60-2.05(4H, m), 2.09 (3H, s),

2.10 (3H, s), 2.30-3.35 (5H, m), 3.41 (3H, s), 3.51-3.61 (2H, m), 3.90-3.97 (1H, m), 4.52-4.58 (1H, m), 7.58 (1H, dd, J = 1.8 and 8.8), 7.89-7.99 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{24}H_{28}ClN_3O_3S \cdot 0.7H_2O$

Calculated (%): C, 59.24; H, 6.09; N, 8.63

Found (%): C, 59.33; H, 6.13; N, 8.34

[0092]

Example 37

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-ethyl-4,5-dimethy-1H-imidazol-2-yl)piperidine

37a) Tert-butyl 4-(1-ethyl-4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate

From tert-butyl 4-(4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.24 g) obtained in Example 35c) and ethyl iodide (134 mg), the title compound (0.27 g, quantitative) was obtained as a brown oil as in a similar manner to Example 34a).

NMR (200 MHz, $CDCl_3$) δ: 1.26 (3H, t, J = 3.6), 1.45 (9H, s), 1.70-2.22 (4H, m), 2.11 (3H, s), 2.12 (3H, s), 2.70-2.90 (3H, m), 3.81 (2H, q, J = 7.0), 4.18-4.25 (2H, m).

37b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-(1-ethyl-4,5-dimethyl-1H-imidazol-2-yl)piperidine

From tert-butyl 4-(1-ethyl-4,5-dimethyl-1H-imidazol-2-yl)-1-piperidinecarboxylate (0.26 g) obtained in Example 37a), the title compound (0.15 g, 36%) was obtained as

colorless powder in a similar manner to Example 1.

NMR (200 MHz, $CDCl_3$) δ: 1.27 (3H, t, J = 7.2), 1.76-3.19(9H, m), 2.10 (6H, s), 3.15-3.61 (2H, m), 3.85 (2H, q, J = 7.2), 3.51-3.61 (2H, m), 3.91-3.99 (1H, m), 4.54-4.61 (1H, m), 7.58 (1H, dd, J = 2.0 and 8.8), 7.94-7.99 (4H, m), 8.49 (1H, s).

Elemental analysis for $C_{25}H_{30}ClN_3O_3S \cdot 0.9H_2O \cdot 0.2C_4H_8O_2$

Calculated (%): C, 59.38; H, 6.45; N, 8.05

Found (%): C, 59.71; H, 6.72; N, 7.83

[0093]

Example 38

Tert-butyl 4-{(2-hydroxyethyl)[(2-methyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate

38a) Tert-butyl 4-[(2-hydroxyethyl)amino]-1-piperidinecarboxylate

A solution of tert-butyl 4-oxo--1-piperidinecarboxylate (15.0 g), 2-aminoethanol (14.0 mL) and acetic acid (6.6 mL) in 1,2-dichloroethane (300 mL) was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (49.2 g) was added thereto, and the mixture was stirred at room temperature for 15 hours. The reaction solution was adjusted to pH 12 with a 1N aqueous sodium hydroxide solution and then extracted with chloroform (100 mL). An organic layer was dried over anhydrous magnesium sulfate and the solvent was then

distilled off under reduced pressure to obtain the title compound (18.0 g, 89%) as a colorless oil.

NMR (200 MHz, $CDCl_3$) δ: 1.17-1.37 (2H, m), 1.46 (9H, s), 1.88 (2H, t), 2.57-2.85 (5H, m), 3.66 (2H, t), 4.06 (2H, d).

38b) Tert-butyl 4-{(2-hydroxyethyl)[(2-methyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate

HOBt (3.7 g) and WSC (4.6 g) were successively added to a suspension of 2-methylimidazole-4-carboxylic acid (2.0 g) in acetonitrile (150 mL), and the mixture was stirred at room temperature for 20 minutes. To this reaction solution was added a solution of tert-butyl 4-[(2-hydroxyethyl)amino]-1-piperidinecarboxylate (4.7 g) obtained in Example 38a) and triethylamine (8.0 mL) in acetonitrile (50 mL), and the mixture was stirred at room temperature for 15 hours. After acetonitrile was distilled off under reduced pressure, chloroform (100 mL) and water (100 mL) were added to the residue. An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate: ethanol = 5:1) to obtain the title compound (1.0 g, 18%) as a colorless oil.

NMR (200 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.84 (4H, bs), 2.37 (2H, bs), 2.78 (2H, bs), 3.82 (4H, bs), 4.27 (3H, bs), 7.31 (1H, bs).

LC/MS: 353 (MH^+).

38c) Tert-butyl 4-(3-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate

Under ice-cooling, methanesulfonic acid chloride (240 µL) was added dropwise to a solution of tert-butyl 4-{(2-hydroxyethyl)[(2-methyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate (940 mg) obtained in Example 38b) and triethylamine (720 µL) in THF (30 mL), and the mixture was stirred at room temperature for 3 hours. To the reaction solution were added chloroform (50 mL) and water (50 mL). An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate: ethanol = 5:1) to obtain the title compound (390 mg, 44%) as a white solid.

NMR (300 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.52-1.72 (4H, s), 2.41 (3H, s), 2.85 (2H, t), 3.57 (2H, t), 4.04 (2H, t), 4.23 (2H, bs), 4.73-4.81 (1H, m), 7.62 (1H, s).

LC/MS: 335 (MH^+).

38d) 7-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-3-methyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one

Concentrated hydrochloric acid (5 mL) was added to tert-butyl 4-(3-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate (420 mg)

obtained in Example 38c) to dissolve it. To this solution was added ethanol (50 mL) and the solvent was distilled off under reduced pressure. To the residue was added ethanol again and the solvent was distilled off under reduced pressure. To the residue was added isopropyl alcohol and a precipitate was filtered. The precipitate was washed successively with isopropyl alcohol and diethyl ether, and dried under reduced pressure to obtain 3-methyl-7-(4-piperidinyl)-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one dihydrochloride as a white solid.

3-[(6-Chloro-2-naphthyl)sulfonyl]propionic acid (400 mg) was suspended in acetonitrile (10 mL) and to the suspension, HOBt(310 mg) and WSC(380 mg) were added successively. The mixture was stirred at room temperature for 20 minutes. To this reaction solution was added a solution of 3-methyl-7-(4-piperidinyl)-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one dihydrochloride obtained in Example 38c), DBU (330 mL) and triethylamine (460 mL) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 15 hours. After acetonitrile was distilled off under reduced pressure, chloroform (50 mL) and water (50 mL) were added to the residue. An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with

a basic silica gel column (ethyl acetate:ethanol = 5:1) and then recrystallized from ethyl acetate:ethanol to obtain the title compound (320 mg, 48%) as a white crystal.

NMR (300 MHz, $CDCl_3$) δ: 1.54-1.67 (11H, m), 1.72-1.85 (2H, m), 2.41 (3H, s), 2.61-2.79 (1H, m), 2.80-2.87 (1H, m), 2.94-3.05 (1H, m), 3.17-3.25 (1H, m), 3.45-3.55 (1H, m), 3.60-3.70 (3H, m), 4.67-4.72 (1H, m), 4.83-4.90 (1H, m), 7.58-7.63 (2H, m), 7.89-7.96 (4H, m), 8.48 (1H, d).

LC/MS: 515 (MH^+).

Elemental analysis for $C_{25}H_{27}ClN_4O_4S$

Calculated (%): C, 58.30; H, 5.28; N, 10.88

Found (%): C, 58.13; H, 5.15; N, 10.67

[0094]

Example 39

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-methyl-6,7-dihydoroimidazo[1,5-a]pyrazin-8(5H)-one

39a) Tert-butyl 4-{(2-hydroxyethyl)[(4-methyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate

HOBt (2.8 g) and WSC (3.5 g) were added successively to a suspension of 4-methylimidazole-4-carboxylic acid hydrochloride (G. Wellmann et al. Synthesis, 356 (1984))(1.6 g) in acetonitrile (100 mL), and the mixture was stirred at room temperature for 20 minutes (reaction solution A). In another flask, a solution of tert-butyl 4-

[(2-hydroxyethyl)amino]-1-piperidinecarboxylate (3.0 g), N-trimethylsilylacetamide (8.1 g) and triethylamine (5.0 mL) in acetonitrile (50 mL) was stirred at room temperature for 20 minutes (reaction solution B). The reaction solution B was added to the reaction solution A, and the mixture was stirred at room temperature for 15 hours. After acetonitrile was distilled off under reduced pressure, chloroform (100 mL) and water (100 mL) were added to the residue. An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate: ethanol = 5:1) to obtain the title compound (2.0 g, 59%) as a colorless oil.

NMR (300 MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.84 (4H, bs), 2.27 (3H, s), 2.77 (2H, bs), 3.68 (2H, bs), 3.79-3.82 (2H, m), 4.20-4.33 (3H, m), 7.32 (1H, s).

LC/MS: 353 (MH^+).

39b) Tert-butyl 4-(1-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate

From tert-butyl 4-{(2-hydroxyethyl)[(4-ethyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate obtained in Example 39a), the title compound (560 mg, 30%) was obtained as a white solid in a similar manner to Example 38c).

NMR (300 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.55-1.71 (4H, m),

2.54 (3H, s), 2.84 (2H, t), 3.55 (2H, t), 4.13 (2H, t), 4.22 (2H, bs), 4.74-4.83 (1H, m), 7.39 (1H, s).

LC/MS: 335 (MH^+).

39c) 7-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-methyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one

From tert-butyl 4-(1-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate obtained in Example 39b), the title compound (475 mg, 46%) was obtained as a white crystal (ethanol/ethyl acetate) in a similar manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.52-1.80 (6H, m), 2.54 (3H, s), 2.57-3.26 (3H, m), 3.43-3.68 (3H, m), 3.97 (1H, d), 4.14 (1H, t), 4.69 (1H, d), 4.81-4.93 (1H, m), 7.41 (1H, s), 7.61 (1H, dd), 7.89-7.98 (4H, m), 8.49 (1H, s).

LC/MS: 515 (MH^+).

Elemental analysis for $C_{25}H_{27}ClN_4O_4S \cdot 0.2EtOAc$

Calculated (%): C, 58.18; H, 5.41; N, 10.52

Found (%): C, 58.01; H, 5.19; N, 10.39

[0095]

Example 40

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-ethyl-6,7-dihydoroimidazo[1,5-a]pyrazin-8(5H)-one

40a) Tert-butyl 4-{(2-hydroxyethyl)[(4-ethyl-1H-imidazol-5-

yl)carbonyl]amino}-1-piperidinecarboxylate

Ethyl 4-ethylimidazole-4-carboxylate (2.3 g) was dissolved in 8N hydrochloric acid (50 mL), and the solution was heated at 100°C for 15 hours. The solvent was distilled off under reduced pressure to obtain 4-ethylimidazole-4-carboxylic acid hydrochloride as a brown solid. Using this brown solid, the title compound (2.5 g, 46%) was obtained as a brown oil in a similar manner to Example 39a).

NMR (200 MHz, $CDCl_3$) δ: 1.14-1.29 (3H, m), 1.46 (9H, s), 1.83 (4H, bs), 2.73-3.02 (4H, m), 3.60-3.81 (4H, m), 4.08-4.39 (3H, m), 7.32 (1H, s).

LC/MS: 367 (MH^+).

40b) Tert-butyl 4-(1-ethyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate

From tert-butyl 4-{(2-hydroxyethyl)[(4-ethyl-1H-imidazol-5-yl)carbonyl]amino}-1-piperidinecarboxylate obtained in Example 40a), the title compound (1.5 g, 62%) was obtained as a brown oil in a similar manner to Example 38c).

NMR (200 MHz, $CDCl_3$) δ: 1.28 (3H, t), 1.46 (9H, s), 1.53-1.75 (4H, m), 2.84 (2H, t), 2.97 (2H, q), 3.52-3.58 (2H, m), 4.11-4.29 (4H, m), 4.73-4.85 (1H, m), 7.42 (1H, s).

LC/MS: 349 (MH^+).

40c) 7-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)-1-ethyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one

Form tert-butyl 4-(1-ethyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate obtained in Example 40b), the title compound (1.3 g, 57%) was obtained as a white crystal (ethyl acetate/diethyl ether) in a similar manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.28 (3H, t), 1.49-1.66 (2H, m), 1.69-1.85 (2H, m), 2.59-2.68 (1H, m), 2.77-2.92 (1H, m), 2.93-3.03 (3H, m), 3.14-3.24 (1H, m), 3.45-3.55 (3H, m), 3.59-3.69 (1H, m), 3.97 (1H, d), 4.10-4.15 (2H, m), 4.74 (1H, d), 4.80-4.90 (1H, m), 7.41 (1H, s), 7.59 (1H, dd), 7.89-7.93 (4H, m), 8.47 (1H, s).

LC/MS: 529 (MH^+).

Elemental analysis for $C_{26}H_{29}ClN_4O_4S \cdot 0.5H_2O \cdot 0.1EtOAc$

Calculated (%): C, 57.98; H, 5.68; N, 10.25

Found (%): C, 58.25; H, 5.64; N, 9.98

[0096]

Example 41

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-ethyl-3-methyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one

41a) 4-Ethyl-2-methyl-1H-imidazole-5-carboxylic acid

4-Ethyl-2-methyl-1H-imidazole-5-carbaldehyde (10 g)

and sodium dihydrogenphosphate (26 g) were suspended in a tert-butanol:water:2-methyl-2-butene = 5:4:1 mixture (200 mL) and to the suspension, sodium chlorite (35 g) was added slowly. The mixture was then stirred at room temperature for 5 hours. After tert-butanol was distilled off under reduced pressure, the residue was adjusted to pH 3 with 1N hydrochloric acid to obtain a precipitate. The precipitate was filtered, washed with diethyl ether and dried under reduced pressure to obtain the title compound (2.8 g, 25%) as a pale yellow solid.

NMR (300 MHz, DMSO-d_6) δ: 1.17 (3H, t), 2.32 (3H, s), 2.56 (2H, q).

41b) Tert-butyl 4-{[(4-ethyl-2-methyl-1H-imidazol-5-yl)carbonyl](2-hydroxyethyl)amino}-1-piperidinecarboxylate

From 4-ethyl-2-methyl-1H-imidazole-5-carboxylic acid obtained in Example 41a), the title compound (3.3 g, 57%) was obtained as a yellow oil in a similar manner to Example 39a).

NMR (300 MHz, $CDCl_3$) δ: 1.24 (3H, t), 1.46 (9H, s), 1.67-1.87 (4H, m), 2.24 (3H, m), 2.61 (2H, q), 2.76-2.83 (4H, m), 3.64 (2H, t), 3.79-3.81 (2H, m).

LC/MS: 381 (MH^+).

41c) Tert-butyl 4-(1-ethyl-3-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate

From tert-butyl 4-{[(4-ethyl-2-methyl-1H-imidazol-5-yl)carbonyl](2-hydroxyethyl)amino}-1-piperidinecarboxylate obtained in Example 41b), the title compound (1.1 g, 35%) was obtained as a yellow oil in a similar manner to Example 38a).

NMR (200 MHz, $CDCl_3$) δ: 1.31 (3H, t), 1.47 (9H, s), 1.67-1.75 (4H, m), 2.52 (3H, s), 2.67 (2H, q), 2.84 (2H, t), 3.50-3.56 (2H, m), 3.91-4.02 (2H, m), 4.21-4.27 (2H, m), 4.72-4.84 (1H, m).

LC/MS: 363 (MH^+).

41d) 7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-ethyl-3-methyl-6,7-dihydroimidazo[1,5-a]pyrazin-8(5H)-one

From tert-butyl 4-(1-ethyl-3-methyl-8-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-1-piperidinecarboxylate obtained in Example 41c), the title compound (740 mg, 45%) was obtained as a white crystal (ethyl acetate/ethanol) in a similar manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, t), 1.50-1.84 (4H, m), 2.51 (3H, s), 2.60-2.70 (3H, m), 2.77-2.87 (1H, m), 2.93-3.04 (1H, m), 3.19 (1H, t), 3.45-3.55 (3H, m), 3.59-3.69 (1H, m), 3.96-4.00 (3H, m), 4.69 (1H, d), 4.85 (1H, tt), 7.59 (1H, dd), 7.89-7.96 (4H, m), 8.48 (1H, d).

LC/MS: 543 (MH^+).

Elemental analysis for $C_{27}H_{31}ClN_4O_4S \cdot 0.1EtOAc$

Calculated (%): C, 59.63; H, 5.81; N, 10.15

Found (%): C, 59.34; H, 5.61; N, 10.16

[0097]

Example 42

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-ethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

42a) Tert-butyl 4-{[(2-ethyl-1H-imidazol-5-yl)methyl]amino}-1-piperidinecarboxylate

After a solution of 2-ethyl-4-formylimidazole (5.0 g), tert-butyl 4-amino-1-piperidinecarboxylate (8.9 g) and acetic acid (1.0 mL) in 1,2-dichloroethane (100 mL) was stirred at room temperature for 1 hour, sodium triacetoxyborohydride (17 g) was added and the mixture was stirred at room temperature for 15 hours. An aqueous saturated sodium hydrogencarbonate solution (100 mL) was added to the reaction solution. An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate: ethanol = 10:1) to obtain the title compound (10 g, 81%) as a yellow oil.

NMR (300 MHz, $CDCl_3$) δ: 1.19-1.31 (5H, m), 1.46 (9H, s), 1.46-1.84 (2H, m), 2.67-2.81 (4H, m), 3.75 (2H, s), 4.04-4.09 (3H, m), 6.73 (1H, s).

LC/MS: 309 (MH^+).

42b) Tert-butyl 4-(5-ethyl-3-oxo-1H-imidazo[1,5-c]imidazol-2(3H)-yl)-1-piperidinecarboxylate

N,N'-carbonyldiimidazole (5.8 g) was added to a solution of tert-butyl 4-{[(2-ethyl-1H-imidazol-5-yl)methyl]amino}-1-piperidinecarboxylate (10 g) obtained in Example 42a) and DBU (5.8 mL) in dichloromethane (100 mL), and the mixture was stirred at room temperature for 5 hours. Water (100 mL) was added to the reaction solution, and an organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified with a silica gel column (ethyl acetate:ethanol = 5:1) to obtain the title compound (4.8 g, 44%) as a colorless oil.

NMR (300 MHz, $CDCl_3$) δ: 1.35 (3H, t), 1.40-1.49 (11H, m), 1.64 (2H, qd), 1.85 (2H, d), 2.83 (2H, t), 3.02 (2H, t), 4.04-4.15 (1H, m), 4.30 (2H, m), 6.72 (1H, t).

LC/MS: 335 (MH^+).

42c) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-ethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

From tert-butyl 4-(5-ethyl-3-oxo-1H-imidazo[1,5-c]imidazol-2(3H)-yl)-1-piperidinecarboxylate obtained in Example 42b), the title compound (1.7 g, 47%) was obtained as a white crystal (ethanol/ethyl acetate) in a similar

manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.35 (3H, t), 1.58-1.75 (2H, m), 1.87-1.99 (2H, m), 2.63 (1H, t), 2.82-2.93 (2H, m), 3.00 (2H, q), 3.19 (1H, t), 3.47-3.65 (1H, m), 3.99 (1H, d), 4.08-4.22 (1H, m), 4.25 (2H, s), 4.72 (1H, d), 6.72 (1H, t), 7.59 (1H, dd), 7.89-7.26 (4H, m), 8.48 (1H, s).

LC/MS: 515 (MH^+).

Elemental analysis for $C_{25}H_{27}ClN_4O_4S \cdot 0.5EtOAc$

Calculated (%): C, 58.00; H, 5.59; N, 10.02

Found (%): C, 57.83; H, 5.32; N, 10.25

[0098]

Example 43

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-methyl-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one hydrochloride

43a) Tert-butyl 4-methyl-4-{[(2-methyl-1H-imidazol-5-yl)methyl]amino}-1-piperidinecarboxylate

From 2-methyl-4-formylimidazole (670 mg) and tert-butyl 4-amino-4-methylpiperidine-1-carboxylate (WO 01/40217) (1.3 g), the title compound (230 mg, 12%) was obtained as a colorless oil in a similar manner to Example 42a).

NMR (200 MHz, $CDCl_3$) δ: 1.18 (3H, s), 1.45 (9H, s), 1.48-1.57 (4H, m), 2.39 (3H, s), 3.36-3.49 (4H, m), 3.66 (2H, s), 6.75 (1H, s).

43b) Tert-butyl 4-methyl-4-(5-methyl-3-oxo-1H-imidazo[1,5-c]imidazol-2(3H)-yl)-1-piperidinecarboxylate

From tert-butyl 4-methyl-4-{[(2-methyl-1H-imidazol-5-yl)methyl]amino}-1-piperidinecarboxylate obtained in Example 43a), the title compound (170 mg, 68%) was obtained as a yellow oil in a similar manner to Example 42b).

NMR (300 MHz, $CDCl_3$) δ: 1.44 (3H, s), 1.46 (9H, s), 1.67-1.80 (2H, m), 2.04 (2H, bs), 2.59 (3H, s), 3.32-3.41 (2H, m), 3.55-3.60 (2H, m), 4.34 (2H, s), 6.66 (1H, s).

LC/MS: 335 (MH^+).

43c) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-methyl-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one hydrochloride

From tert-butyl 4-methyl-4-(5-methyl-3-oxo-1H-imidazo[1,5-c]imidazol-2(3H)-yl)-1-piperidinecarboxylate obtained in Example 43b), 2-(1-{3-[6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-methyl-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one was obtained as a colorless oil in a similar manner to Example 38d). This oil was dissolved in ethyl acetate (2 mL) and thereto a 4N solution of hydrogen chloride in ethyl acetate (200 μL) was added. The mixture was stirred at room temperature for 10 minutes. A Precipitate was filtered, washed successively with ethyl acetate and diethyl ether, and dried under reduced pressure to obtain the title

compound (153 mg, 51%) as a white solid.

NMR (200 MHz, $CDCl_3$) δ: 1.54 (3H, s), 1.75-2.02 (2H, m), 2.17-2.25 (1H, m), 2.47-2.55 (1H, m), 2.85-2.92 (2H, m), 2.96 (3H, s), 3.46-3.63 (6H, m), 4.65 (2H, s), 7.22 (1H, s), 7.57-7.62 (1H, m), 7.88-7.98 (4H, m), 8.48 (1H, s).

LC/MS: 515 (MH^+).

Elemental analysis for $C_{25}H_{27}ClN_4O_4S \cdot HCl$

Calculated (%): C, 51.90; H, 5.40; N, 9.68

Found (%): C, 52.16; H, 5.55; N, 9.81

[0099]

Example 44

2-(1-{3-[(4-Bromophenyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

From 3-[(4-bromophenyl)sulfonyl]propionic acid (WO 98/05635) (1.1 g) and 5-methyl-2-(4-piperidinyl)-1,2-dihydro-3H-imidazo[1,5-c]imidazole (1.0 g) obtained in Example 69b), the title compound (720 mg, 39%) was obtained as a white crystal (chloroform/diethyl ether) in a similar manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.56-1.77 (2H, m), 1.88-2.05 (2H, m), 2.61 (3H, s), 2.66-2.70 (1H, m), 2.76-2.99 (2H, m), 3.15-3.25 (1H, m), 3.38-3.59 (2H, m), 3.98 (1H, d), 4.18 (1H, m), 4.27 (2H, s), 4.73 (1H, d), 6.71 (1H, t), 7.71-7.80 (4H, m).

LC/MS: 495 (MH^+).

Elemental analysis for $C_{20}H_{23}BrN_4O_4S \cdot H_2O$

Calculated (%): C, 46.79; H, 4.91; N, 10.91

Found (%): C, 47.09; H, 4.77; N, 11.03

[0100]

Example 45

6-(4-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-1-piperidinyl)-2-methyl-6,7-dihydro-5H-imidazo[1,5-a]imidazol-5-one

45a) 4-Methylimidazole-2-carbaldehyde

According to the article (N. J. Curtis et al. J. Org. Chem., 45, 4038 (1980)), the title compound was synthesized from 4-methylimidazole (99%).

NMR (300 MHz, DMSO-d_6) δ: 2.23 (3H, s), 6.81 (1H, s), 9.51 (1H, s).

45b) Tert-butyl 4-{[(4-methyl-1H-imidazol-2-yl)methyl]amino}piperidine-1-carboxylate

From 4-methylimidazole-2-carbaldehyde (3.4 g) obtained in Example 45a) and tert-butyl 4-aminopiperidine-1-carboxylate (6.3 g), the title compound (6.3 g, 68%) was obtained as a yellow oil in a similar manner to Example 42a).

NMR (300 MHz, $CDCl_3$) δ: 1.16-1.29 (2H, m), 1.45 (9H, s), 1.84 (2H, d), 2.22 (3H, s), 2.59-2.66 (1H, m), 2.76 (2H, t), 3.89 (2H, s), 4.00 (2H, bs), 6.63 (1H, s).

45c) Tert-butyl 4-(2-methyl-5-oxo-5H-imidazo[1,5-

a]imidazol-6(7H)-yl)-1-piperidinecarboxylate

From tert-butyl 4-{[(4-methyl-1H-imidazol-2-yl)methyl]amino}-1-piperidinecarboxylate obtained in Example 45b), the title compound (1.2 g, 46%) was obtained as a yellow oil in a similar manner to Example 42b).

NMR (300 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.56-1.70 (2H, m), 1.85 (2H, d), 2.28 (3H, s), 2.82 (2H, t), 4.10-4.24 (3H, m), 4.27 (2H, s), 7.00 (1H, s).

45d) 6-(4-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-1-piperidinyl)-2-methyl-6,7-dihydro-5H-imidazo[1,5-a]imidazol-5-one

From tert-butyl 4-(2-methyl-5-oxo-5H-imidazo[1,5-a]imidazol-6(7H)-yl)-1-piperidinecarboxylate obtained in Example 45c), the title compound (950 mg 51%) was obtained as a white crystal (ethyl acetate/ethanol) in a similar manner to Example 38b).

NMR (300 MHz, $CDCl_3$) δ: 1.53-1.75 (2H, m), 1.88-2.01 (2H, m), 2.28 (3H, s), 2.62 (1H, t), 2.81-3.02 (2H, m), 3.18 (1H, t), 3.47-3.64 (2H, m), 3.99 (1H, d), 4.18-4.27 (3H, m), 4.71 (1H, d), 7.01 (1H, d), 7.59 (1H, dd), 7.89-7.96 (4H, m), 8.47 (1H, d).

LC/MS: (501 (MH^+).

Elemental analysis for $C_{24}H_{25}N_4O_4SCl \cdot 0.1EtOAc$

Calculated (%): C, 57.48; H, 5.10; N, 10.99

Found (%): C, 57.19; H, 5.17; N, 11.01

[0101]

Example 46

6-(4-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-1-piperidinyl)-2-methyl-6,7-dihydro-5H-imidazo[1,5-a]imidazol-5-one hydrochloride

46a) Tert-butyl 4-hydroxy-4-(7-oxo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-6-yl)-1-piperidinecarboxylate

Under argon atmosphere, a solution of bis(trimethylsilyl)amidolithium in hexane (1.0 M, 13 mL) was diluted with THF(10 mL) and then cooled to -60°C. To this solution was added dropwise a solution of 5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one(C. Christine et al. Tetrahedron, 56, 1837 (2000))(1.0 g) in THF (50 mL) at -60°C. The mixture was stirred at that temperature for 2 hours. To the mixture were added a suspension of anhydrous cerium chloride (3.0 g) in THF (20 mL) at -60°C and then a solution of tert-butyl 4-oxo-1-piperidinecarboxylate (1.4 g) in THF (20 mL) dropwise, and the mixture was stirred at the same temperature for 3 hours. After addition of an aqueous saturated ammonium chloride solution (50 mL) at -60°C, the mixture was warmed to room temperature and then extracted with chloroform (50 mL). An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified with a basic silica gel column (ethyl acetate) to obtain

the title compound (1.2 g, 52%) as a white solid.

NMR (300 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.48-1.71 (2H, m), 3.15 (2H, bs), 3.37 (1H, dd), 3.69-3.92 (4H, m), 4.24 (1H, dd), 4.48 (1H, dd), 7.60 (1H, s), 7.74 (1H, s).

LC/MS: 322 (MH^+).

46b) 6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one hydrochloride

Tert-butyl 4-hydroxy-4-(7-oxo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-6-yl)-1-piperidinecarboxylate (480 mg) obtained in Example 46a) was dissolved in concentrated hydrochloric acid (10 mL), and the solution was heated at 100°C for 15 hours. After the solution was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was dissolved in a mixed solvent (10 mL) of methanol:water = 1:1 and to the solution 10% Pd/C (50 mg) was added. The mixture was stirred for 3 hours under hydrogen atmosphere. The reaction solution was filtered using Celite and the filtrate was concentrated under reduced pressure to obtain 6-(4-piperidinyl)-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one dihydrochloride as a brown solid. From this compound, the title compound (300 mg, 34%) was obtained as a white solid in a similar manner to Example 43c).

NMR (300 MHz, $CDCl_3$) δ: 1.17-1.55 (3H, m), 1.78-1.97 (1H,

m), 2.29-2.55 (2H, m), 2.73-3.03 (3H, m), 3.41-3.57 (3H, m), 3.88 (1H, bs), 4.53 (1H, bs), 4.71 (1H, bs), 4.95 (1H, bs), 7.58 (1H, dd), 7.86-7.99 (5H, m), 8.47 (1H, s), 9.66 (1H, s).

LC/MS: 486 (MH^+).

Elemental analysis for $C_{24}H_{24}N_3O_4SCl \cdot HCl \cdot 0.5H_2O$

Calculated (%): C, 54.24; H, 4.93; N, 7.91

Found (%): C, 54.37; H, 4.93; N, 7.86

[0102]

Example 47

6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-hydroxy-4-piperidinyl)-1-methyl-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one

47a) 1-Methyl-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one

The title compound was synthesized from 4-methyl-1H-imidazole-5-carbaldehyde according to a method described in the article (C. Christine et al. Tetrahedron, 56, 1837 (2000)) (yield 8.5%).

NMR (300 MHz, $CDCl_3$) δ: 2.44 (3H, s), 3.19 (2H, t), 4.31 (2H, t), 7.58 (1H, s).

47b) Tert-butyl 4-hydroxy-4-(1-methyl-7-oxo-6,7-dihydoro-5H-pyrrolo[1,2-c]imdazol-6-yl)-1-piperidinecarboxylate

From 1-methyl-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one (500 mg) obtained in Example 47a), the title compound (790 mg, 64%) was obtained as a white solid in a similar

manner to Example 46a).

NMR (300 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.48-1.76 (4H, m), 3.15-3.21 (2H, m), 3.82-3.95 (2H, m), 4.09 (1H, dd), 4.39 (1H, dd), 7.60 (1H, s).

LC/MS: 336 (MH^+).

47c) 6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-hydroxy-4-piperidinyl)-1-methyl-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one

From tert-butyl 4-hydroxy-4-(1-methyl-7-oxo-6,7-dihydoro-5H-pyrrolo[1,2-c]iimdazol-6-yl)-1-piperidinecarboxylate obtained in Example 47b), the title compound (170 mg, 50%) was obtained as a white crystal (ethyl acetate/ethanol/diethyl ether) in a similar manner to Example 38d).

NMR (300 MHz, $CDCl_3$) δ: 1.46-1.89 (2H, m), 2.44 (3H, s), 2.83-3.06 (3H, m), 3.32-3.73 (6H, m), 3.97-4.12 (2H, m), 4.39 (2H, dd), 7.58-7.61 (2H, m), 7.88-7.98 (4H, m), 8.48 (1H, m).

LC/MS: 516 (MH^+).

Elemental analysis for $C_{25}H_{26}N_3O_5SCl \cdot 0.6H_2O$

Calculated (%): C, 57.00; H, 5.20; N, 7.98

Found (%): C, 56.79; H, 5.28; N, 7.83

[0103]

Example 48

6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)-1-methyl-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one hydrochloride

From tert-butyl 4-hydroxy-4-(1-methyl-7-oxo-6,7-dihydoro-5H-pyrrolo[1,2-c]iimdazol-6-yl)-1-piperidinecarboxylate obtained in Example 47b), the title compound (411 mg, 38%) was obtained as a white solid in a similar manner to Example 46b).

NMR (300 MHz, $CDCl_3$) δ: 1.31-1.40 (1H, m), 1.51-1.56 (1H, m), 1.80-1.98 (1H, m), 2.28 (1H, bs), 2.50 (1H, t), 2.62 (3H, s), 2.75-3.09 (3H, m), 3.25-3.31 (1H, m), 3.44-3.60 (2H, m), 3.88-3.89 (1H, m), 4.52-4.57 (2H, m), 4.78-4.87 (1H, m), 7.59 (1H, d), 7.88-7.97 (4H, m), 8.47 (1H, s), 9.54-9.58 (1H, m).

Elemental analysis for $C_{25}H_{27}N_3O_4SCl_2 \cdot 1.5H_2O$

Calculated (%): C, 53.29; H, 5.37; N, 7.46

Found (%): C, 53.08; H, 5.31; N, 7.65

[0104]

Example 49

6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-7-ol

Acetic acid (2 mL) and sodium cyanoborohydride (390 mg) were added successively to a solution of 6-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6-dihydro-7H-pyrrolo[1,2-c]imidazol-7-one hydrochloride (200 mg) obtained in Example 46b) in dichloroethane (3 mL), and

the mixture was stirred at room temperature for 2 hours. An aqueous saturated sodium hydrogencarbonate solution (30 mL) was added to the reaction solution, and extracted with ethyl acetate (30 mL). An organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified with a basic silica gel column (ethyl acetate:ethanol = 5:1) and recrystallized from ethyl acetate/ethanol to obtain the title compound (45 mg, 24%) as a white crystal.

NMR (300 MHz, $CDCl_3$) δ: 1.12-1.38 (2H, m), 1.57-2.20 (5H, m), 2.48-2.60 (1H, m), 2.66-2.68 (1H, m), 2.83-2.89 (1H, m), 2.98-3.18 (1H, m), 3.54-3.64 (2H, m), 3.84-3.85 (1H, m), 4.06-4.24 (1H, m), 4.53-4.57 (1H, m), 4.98-4.99 (1H, m), 6.82 (1H, bs), 7.38 (1H, bs), 7.56-7.60 (1H, m), 7.88-7.95 (4H, m), 8.46 (1H, s).

Elemental analysis for $C_{24}H_{26}N_3O_4SCl \cdot 0.5H_2O \cdot 0.1EtOAc$

Calculated (%): C, 57.94; H, 5.54; N, 8.31

Found (%): C, 58.04; H, 5.53; N, 8.04

[0105]

Example 50

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1H-imidazol-4-carboxamide

50a) 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine

From 4-aminopiperidine (26 g) and benzaldehyde (27 mL), N-phenylmethylidene-4-piperidinylamine (49 g, quantitative) was synthesized according to a method described in the article (Synthetic Communications, 22, 1357-2360(1992)), and was used in the next reaction without purification.

WSC (1.7 g) was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (2.4 g), N-phenylmethylidene-4-piperidinylamine (1.5 g) and HOBt (1.3 g) in dichloromethane (50 mL), and the mixture was stirred at room temperature for 16 hours. 1 N HCl (30 mL) was added to the reaction solution, and the mixture was stirred at room temperature for 8 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a basic silica gel column to obtain the title compound (2.0 g, 59%) as an oil.

NMR (200 MHz, $CDCl_3$) δ: 1.59-1.70 (4H, m), 1.77-1.92 (2H, m), 2.62-2.75 (1H, m), 2.84-3.02 (2H, m), 3.06-3.25 (2H, m), 3.48-3.60 (2H, m), 3.76-3.84 (1H, m), 4.32-4.40 (1H, m), 7.59 (1H, dd, J = 8.8, 1.8), 7.93-7.98 (4H, m), 8.48 (1H, s).

50b) N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1H-imidazole-4-carboxamide

WSC (0.16 g) was added to a solution of 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (0.29 g) obtained in Example 50a), imidazole-4-carboxylic acid (0.08 g) and HOBt (0.13 g) in dichloromethane (30 mL), and the mixture was stirred at room temperature for 16 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a basic silica gel column to obtain the title compound (47 mg, 13%) as white powder. NMR (300 MHz, $CDCl_3$) δ: 1.13-1.45 (2H, m), 1.92-2.08 (2H, m), 2.74 (1H, t, J = 11.7), 2.82-2.89 (2H, m), 3.15 (1H, t, J = 11.7), 3.52-3.57 (2H, m), 3.78-3.82 (1H, m), 4.10-4.13 (1H, m), 4.36-4.41 (1H, m), 7.17-7.20 (1H, br), 7.56-7.59 (3H, m), 7.86-7.94 (4H, m), 8.45 (1H, s).

[0106]

Example 51

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1H-imidazol-4-yl)methyl-4-piperidineamine

Sodium triacetoxyborohydride (1.3 g) was added to a solution of 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (2.0 g) obtained in Example 50a), 1-tritylimidazole-4-carbaldehyde (1.8 g) and acetic acid (0.3 mL) in 1,2-dichloroethane (30 mL), and the mixture was

stirred at room temperature for 3 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a basic silica gel column to obtain 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1-trithylimidazol-4-yl)methyl-4-piperidineamine (3.0 g, 84%). This intermediate (0.5 g) was dissolved in methanol (10 mL) and 1N hydrochloric acid (5 mL), and then stirred at 90°C for 3 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a basic silica gel column to obtain the title compound (62 mg, 19%) as white powder.

NMR (300 MHz, $CDCl_3$) δ: 1.15-1.29 (2H, m), 1.79-1.93 (2H, m), 2.62-2.86 (4H, m), 2.97-3.09 (1H, m), 3.48-3.56 (2H, m), 3.63-3.75 (3H, m), 4.24-4.31 (1H, m), 6.85 (1H, s), 7.52-7.57 (2H, m), 7.87-7.93 (4H, m), 8.43(1H, s).

[0107]

Example 52

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-(2-methyl-1H-imidazol-4-yl)methyl-4-piperidineamine

52a) 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(2-

methyl-1-trithylimidazol-4-yl)methyl]piperidine-4-amine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (4.0 g) obtained in Example 50a) and 2-methyl-1-trithylimidazole-4-carbaldehyde (3.7 g), the title compound (1.9 g, 24%) was prepared as white powder according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.21-1.28(2H, m), 1.61(3H, s), 1.81-2.03(2H, m), 2.61-2.88(4H, m), 2.98-3.11(1H, m), 3.47-3.57(2H, m), 3.63(2H, s), 3.75-3.81(1H, m), 4.28-4.34(1H, m), 6.57(1H, s), 7.10-7.31(15H, m), 7.33-7.60(1H, m), 7.91-7.96(4H, m), 8.46(1H, s).

52b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(2-methyl-1H-imidazol-4-yl)methyl]piperidine-4-amine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(2-methyl-1-tritylimidazol-4-yl)methylpiperidine-4-amine (0.4 g) obtained in Example 52a), the title compound (0.23 g, 87%) was prepared as white powder according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.19-1.31 (2H, m), 1.83-1.96 (2H, m), 2.37 (3H, s), 2.68-2.91 (4H, m), 3.00-3.13 (1H, m), 3.51-3.60 (2H, m), 3.72-3.82 (3H, m), 4.28-4.34 (1H, m), 6.74 (1H, s), 7.61 (1H, dd, J = 8.2, 1.8), 7.87-7.97(4H, m), 8.47(1H, m).

[0108]

Example 53

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(4-methyl-1H-imidazol-5-yl)methyl]-4-piperidineamine

53a) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (2.0 g) obtained in Example 50a) and 4-methyl-1-tritylimidazole-4-carbaldehyde (1.9 g), the title compound (2.2 g, 59%) was prepared as white powder according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.21-1.29(2H, m), 1.39(3H, s), 1.78-1.98(2H, m), 2.66-2.89(4H, m), 2.97-3.14(1H, m), 3.49-3.57(2H, m), 3.65(2H, s), 3.71-3.80(1H, m), 4.26-4.32(1H, m), 7.11-7.32(16H, m), 7.54-7.59(1H, m), 7.91-7.95(4H, m), 8.46(1H, s).

53b) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(4-methyl-1H-imidazol-5-yl)methyl]-4-piperidineamine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (0.7 g) obtained in Example 53a), the title compound (0.20 g, 76%) was prepared as white powder according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.20-1.30 (2H, m), 1.78-1.98 (2H, m), 2.15 (3H, s), 2.65-2.87 (4H, m), 2.95-3.12 (1H, m), 3.45-3.58 (2H, m), 3.67-3.78 (3H, m), 4.23-4.30 (1H, m), 5.01-5.68 (1H, br), 7.36-7.41 (1H, m), 7.54 (1H, dd), 7.88-

7.93 (4H, m), 8.44(1H, s).

[0109]

Example 54

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1H-imidazol-2-yl)methyl-4-piperidineamine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (0.5 g) obtained in Example 50a) and imidazole-2-carbaldehyde (0.13 g), the title compound (0.54 g, 90%) was prepared as white powder according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.02-1.48 (2H, m), 1.80-2.03 (2H, m), 2.69-3.06 (5H, m), 3.53-3.60 (2H, m), 3.75-3.96 (3H, m), 4.29-4.43 (1H, m), 7.02 (1H, s), 7.04 (1H, s), 7.51(1H, dd), 7.93-7.98 (4H, m), 8.49(1H, s).

[0110]

Example 55

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-N-(1H-imidazol-4-yl)methylacetamide

Acetyl chloride (0.068 mL) was added to a solution of 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1-tritylimidazol-4-yl)methyl-4-piperidineamine (0.6 g) obtained in Example 51 and triethylamine (0.24 mL) in dichloromethane (30 mL) under ice-cooling, and the mixture was stirred at room temperature for 16 hours. After the solvent was distilled off, trifluoroacetic acid (5 mL) was

added to the residue and the reaction solution was stirred at room temperature for 1 hour. After the solvent was distilled off, the residue was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a basic silica gel column to obtain the title compound (68 mg, 16%) as pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.52-1.84 (4H, m), 2.15 (3H, d), 2.44-2.60 (1H, m), 2.79-3.10 (3H, m), 3.49-3.56 (2H, m), 3.58-4.07 (2H, m), 4.32-4.37 (2H, m), 4.49-4.63 (1H, m), 6.79-6.89 (1H, m), 7.47-7.59 (2H, m), 7.89-7.95 (4H, m), 8.43-8.46 (1H, m).

[0111]

Example 56

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-N-(1H-imidazol-4-yl)methylmethanesulfonamide

Methanesulfonyl chloride (0.074 mL) was added to a solution of 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1-tritylimidazol-4-yl)methyl-4-piperidineamine (0.6 g) obtained in Example 51 and triethylamine (0.24 mL) in dichloromethane (30 mL) under ice-cooling, and the mixture was stirred at room temperature for 16 hours. After the solvent was distilled off, trifluoroacetic acid (5 mL) was

added to the residue and the reaction solution was stirred at room temperature for 1 hour. After the solvent was distilled off, the residue was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a basic silica gel column to obtain the title compound (90 mg, 19%) to obtain pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.58-1.87 (4H, m), 2.17 (3H, s), 2.30-2.48 (1H, m), 2.64-3.09 (3H, m), 3.47-3.63 (2H, m), 3.72-3.94 (2H, m), 4.21-4.39 (2H, m), 4.51-4.57 (1H, m), 6.97 (1H, s), 7.51-7.55 (2H, m), 7.82-7.92 (4H, m), 8.42 (1H, s).

[0112]

Example 57

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-ethyl-N-[(2-methyl-1H-imidazol-4-yl)methyl]-4-piperidineamine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(2-methyl-1-tritylimidazol-4-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 52a) and acetoaldehyde (0.05 mL), the title compound (0.23 g, 65%) was obtained as pale yellow powder in a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.03 (3H, t), 1.32-1.46 (2H, m), 1.72-1.86 (2H, m), 2.38 (3H, s), 2.46-2.58 (3H, m), 2.69-

3.02 (4H, m), 3.52-3.60 (4H, m), 3.81-3.88 (1H, m), 4.49-4.56 (1H, m), 6.72 (1H, s), 7.29(1H, d), 7.58 (1H, dd), 7.92-7.97 (4H, m), 8.47 (1H, s).

[0113]

Example 58

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-N-(2-methyl-1H-imidazol-4-yl)methylacetaimde

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(2-methyl-1-tritylimidazol-4-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 52a) and acetyl chloride (0.06 mL), the title compound (0.11 g, 31%) was obtained as pale yellow powder in a similar manner to Example 55.

NMR (200 MHz, $CDCl_3$) δ: 1.25-1.77 (4H, m), 2.16 (3H, s), 2.33 (3H, s), 2.41-2.48 (1H, m), 2.58-3.05 (3H, m), 3.49-3.58 (2H, m), 3.79-4.03 (1H, m), 4.27-4.32 (2H, m), 4.56-4.67 (2H, m), 6.68(1H, d), 7.54-7.60 (1H, m), 7.89-7.97 (4H, m), 8.44-8.48 (1H, m).

[0114]

Example 59

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-3-methyl-7,8-dihydroimidazo[1,5-a]pyrazin-6(5H)-one

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(2-methyl-1-tritylimidazol-4-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 52a) and chloroacetyl chloride

(0.1 mL), the title compound (0.08 g, 24%) was obtained as white crystals in a similar manner to Example 55.

NMR (200 MHz, $CDCl_3$) δ: 1.60-1.80 (4H, m), 2.38(3H, s), 2.63-2.72 (1H, m), 2.86-2.99 (2H, m), 3.10-3.29 (1H, m), 3.50-3.64 (2H, m), 3.97-4.03 (1H, m), 4.42 (2H, s), 4.55 (2H, s), 4.69-4.82 (2H, m), 6.80 (1H, s), 7.62 (1H, dd), 7.90-7.99 (4H, m), 8.50 (1H, s).

[0115]

Example 60

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-N-(4-methyl-1H-imidazol-5-yl)methylacetamide

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 53a) and acetyl chloride (0.06 mL), the title compound (0.10 g, 28%) was obtained as pale yellow powder in a similar manner to Example 55.

NMR (200 MHz, $CDCl_3$) δ: 1.60-1.78 (4H, m), 2.18 (3H, s), 2.19 (3H, s), 2.49-2.55 (1H, m), 2.78-3.08 (3H, m), 3.48-3.62 (2H, m), 3.65-4.05 (1H, m), 4.24-4.39 (2H, m), 4.48-4.65 (2H, m), 7.34-7.43 (1H, m), 7.57 (1H, dd), 7.91-7.97 (4H, m), 8.45-8.47 (1H, m).

[0116]

Example 61

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-ethyl-N-(4-methyl-1H-imidazol-5-yl)methyl-4-piperidineamine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 53a) and acetoaldehyde (0.05 mL), the title compound (0.14 g, 40%) was obtained as pale yellow powder in a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 0.99 (3H, t), 1.32-1.47 (2H, m), 1.71-1.84 (2H, m), 2.18 (3H, s), 2.38-2.55 (3H, m), 2.70-2.94 (4H, m), 3.52-3.58 (4H, m), 3.82-3.88 (1H, m), 4.49-4.56 (1H, m), 7.55 (1H, s), 7.57 (1H, dd), 7.92-7.96 (4H, m), 8.47 (1H, s).

[0117]

Example 62

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-7,8-dihydroimidazo[1,2-a]pyrazin-6(5H)-one

From 1-(3{[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(1H-imidazol-2-yl)methyl-4-piperidineamine (0.5 g) obtained in Example 54 and chloroacetyl chloride (0.1 mL), the title compound(0.03 g, 5%) was obtained as colorless powder in a similar manner to Example 55.

NMR (200 MHz, $CDCl_3$) δ: 1.61-1.81 (4H, m), 2.56-2.72 (1H, m), 2.87-2.97 (2H, m), 3.11-3.28 (1H, m), 3.54-3.62 (2H, m), 3.97-4.09 (1H, m), 4.49 (2H, s), 4.69-4.78 (4H, m), 6.89 (1H, s), 7.11 (1H, s), 7.60 (1H, dd), 7.95-7.99 (4H, m), 8.49 (1H, s).

[0118]

Example 63

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

From N-tert-butylcarbonyl-4-piperidinylamine (2.0 g) and 2-methyl-1-tritylimidazole-4-carbaldehyde (3.5 g), N-tert-butylcarbonyl-(2-methyl-1-tritylimidazol-4-yl)methyl-4-piperidineamine (4.0 g, 75%) was obtained in a similar manner to Example 51. Then, from this compound and chloroacetyl chloride (1.1 mL), N-tert-butyl-3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (2.0 g, 80%) was obtained in a similar manner to Example 59. This compound was dissolved in THF (20 mL) and a 1 M solution of borane/THF complex in THF (18 mL) was added. The mixture was heated to reflux overnight. After 1N hydrochloric acid (20 mL) was added, the mixture was stirred and then concentrated. The residue was dissolved in trifluoroacetic acid (15 mL), de-tert-butoxycarbonylated, and then condensed with 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (1.7 g) to obtain the title compound(0.04 g, 1.4%) as pale yellow powder in a similar manner to Example 50b). NMR (200 MHz, $CDCl_3$) δ: 1.17-1.48 (2H, m), 1.80-1.94 (2H, m), 2.27 (3H, s), 2.58-2.63 (2H, m), 2.81-2.89 (4H, m), 2.98-3.12 (1H, m), 3.42-3.56 (2H, m), 3.70-3.81 (5H, m), 4.43-4.50 (1H, m), 6.59 (1H, s), 7.54 (1H, dd), 7.89-7.93

(4H, m), 8.44 (1H, s).

[0119]

Example 64

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1,5-dimethyl-7,8-dihydroimidazo[1,5-a]pyrazin-6(5H)-one

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (1.5 g) obtained in Example 53a) and 2-chloropropionyl chloride (0.24 mL), the title compound (0.66 g, 62%) was obtained as white crystals in a similar manner to Example 59.

NMR (200 MHz, $CDCl_3$) δ: 1.16 (3H, d), 1.69-1.76 (4H, m), 2.20 (3H, s), 2.48-2.78 (1H, m), 2.93-3.02 (2H, m), 3.11-3.30 (1H, m), 3.53-3.73 (2H, m), 3.98-4.05 (1H, m), 4.33 (2H, s), 4.72-4.78 (3H, m), 7.46 (1H, s), 7.62 (1H, dd), 7.96-7.99 (4H, m), 8.51 (1H, s).

[0120]

Example 65

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-7-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (1.5 g) obtained in Example 53a) was dissolved in 1N

hydrochloric acid (20 mL), and the solution was stirred at 70°C for 4 hours. After cooled, the reaction solution was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was dissolved in dichloromethane (20 mL), and DBU (0.16 mL) and carbonyldiimidazole (0.19 g) were added. The reaction solution was stirred overnight and poured into an aqueous potassium carbonate solution. The reaction solution was extracted with chloroform and the extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a silica gel column to obtain the title compound (83 mg, 7%) as a white crystal.

NMR (200 MHz, $CDCl_3$) δ: 1.64-1.88 (2H, m), 1.96-2.04 (2H, m), 2.24 (3H, s), 2.60-2.73 (1H, m), 2.87-3.01 (2H, m), 3.15-3.27 (1H, m), 3.46-3.73 (2H, m), 3.99-4.33 (2H, m), 4.28 (2H, s), 4.71-4.78 (1H, m), 7.62 (1H, dd), 7.87-8.00 (4H, m), 8.51 (1H, s).

[0121]

Example 66

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-methyl-7,8-dihydroimidazo[1,5-a]pyrazin-6(5H)-one

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(4-methyl-1-tritylimidazol-5-yl)methyl]-4-piperidineamine (0.5 g) obtained in Example 53a) and acetyl chloride (0.1 mL), the title compound (0.11 g, 30%) was obtained as white crystals in a similar manner to Example 59.

NMR (200 MHz, $CDCl_3$) δ: 1.67-1.81 (4H, m), 2.19 (3H, s), 2.59-2.72 (1H, m), 2.87-3.02 (2H, m), 3.08-3.32 (1H, m), 3.50-3.65 (2H, m), 3.99-4.08 (1H, m), 4.19 (2H, s), 4.67 (2H, s), 4.71-4.82 (2H, m), 7.44 (1H, s), 7.62 (1H, dd), 7.90-7.99 (4H, m), 8.50 (1H, s).

[0122]

Example 67

7-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine

From N-tert-butylcarbonyl-4-piperidinylamine (2.0 g) and 5-methyl-1-tritylimidazole-4-carbaldehyde (3.5 g), N-tert-butylcarbonyl-[(5-methyl-1-tritylimidazol-4-yl)methyl]-4-piperidineamine (4.5 g, 84%) was obtained in a similar manner to Example 51. Then, from this compound (3.0 g) and bromoacetyl chloride (1.4 mL), N-tert-butyl 4-(1-methyl-6-oxo-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)piperidine-1-carboxylate (2.0 g, 67%) was obtained in a similar manner to Example 59. This compound was dissolved in THF (20 mL) and a 1 M solution of borane/THF complex in

THF (18 mL) was added. The mixture was heated to reflux overnight. After 1N hydrochloric acid (20 mL) was added, the reaction solution was stirred and then concentrated. The residue was dissolved in trifluoroacetic acid (15 mL), de-tert-butoxycarbonylated, and then condensed with 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (1.7 g) to obtain the title compound (0.12 g, 4%) as pale yellow powder in a similar manner to Example 50b).

NMR (200 MHz, $CDCl_3$) δ: 1.39-1.57 (2H, m), 1.85-1.99 (2H, m), 2.11 (3H, s), 2.56-2.94 (6H, m), 3.02-3.14 (1H, m), 3.53-3.60 (2H, m), 3.69 (2H, s), 3.71-3.82 (1H, m), 3.89-4.00 (2H, m), 4.50-4.57 (1H, m), 7.30 (1H, d), 7.58 (1H, dd), 7.93-7.97 (4H, m), 8.48 (1H, s).

[0123]

Example 68

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(4-methyl-1-tritylimidazol-5-yl)methyl]-4-piperidineamine (1.5 g), DBU (0.16 mL) and carbonyldiimidazole (0.19 g), the title compound (0.14 g, 52%) was obtained as white crystals in a similar manner to Example 65.

NMR (200 MHz, $CDCl_3$) δ: 1.58-1.72 (2H, m), 1.86-1.99 (2H, m), 2.61 (3H, s), 2.63-2.68 (1H, m), 2.81-3.01 (2H, m),

3.14-3.23 (1H, m), 3.46-3.65 (2H, m), 3.97-4.02 (1H, m), 4.13-4.22 (1H, m), 4.25 (2H, s), 4.69-4.74 (1H, m), 6.70 (1H, d), 7.59 (1H, dd), 7.89-7.96 (4H, m), 8.47 (1H, d).

[0124]

Example 69

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

69a) 2-(1-Benzyl-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

Under ice-cooling, sodium triacetoxyborohydride (31.8 g) was added to a solution of 2-methylimidazole-4-carbaldehyde (11.0 g), 1-benzylpiperidine-4-amine (19.0 g) and acetic acid (6.7 mL) in 1,2-dichloroethane (200 mL), and the mixture was stirred at room temperature overnight. The reaction solution was washed with an aqueous potassium carbonate solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was dissolved in THF (200 mL), and N, N'-carbonylimidazole (17.8 g) and DBU (16.7 g) were added. The mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated and water was added. After extraction with ethyl acetate, the extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to

obtain the title compound (18.5 g, 60%).

NMR (200 MHz, $CDCl_3$) δ: 1.74-1.85 (4H, m), 2.07-2.20 (2H, m), 2.61 (3H, s, Me), 2.97-3.03 (2H, m), 3.53 (2H, s), 3.89-4.06 (1H, m), 4.30 (2H, s), 6.70 (1H, s), 7.32 (5H, m).

69b) 5-Methyl-2-(4-piperidinyl)-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

2-(1-Benzyl-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one (18.2 g) obtained in Example 69a) and 10% Pd/C (50% hydrous :1.5 g) were added to methanol (300 mL), and the mixture was stirred for 2.5 days under hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated. The residue was recrystallized from ethyl acetate-hexane to obtain the title compound (10.7 g, 83%).

NMR (200 MHz, $CDCl_3$) δ: 1.56-1.89 (4H, m), 2.62 (3H, s, Me), 2.75 (2H, dt), 3.17-3.23 (2H, m), 3.97-4.13 (1H, m), 4.32 (2H, s), 6.71 (1H, s).

69c) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

Under ice-cooling, a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl chloride (14.7 g) obtained in Example 71d) in THF (100 mL) was added dropwise to a solution of 5-methyl-2-(4-piperidinyl)-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one (8.8 g) obtained in Example

69b) and triethylamine (6.7 mL) in THF (150 mL). The reaction solution was stirred at 0°C for 5 hours and the solvent was then distilled off. The residue was diluted with water and extracted with ethyl acetate-THF. The extract was washed with water and then dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a silica gel column and the product was recrystallized from ethyl acetate-methanol to obtain the title compound (11.2 g, 51%) as colorless crystals.

Elemental analysis for $C_{24}H_{25}N_4O_4SCl$

Calculated (%): C, 57.54; H, 5.03; N, 11.18

Found (%): C, 57.42; H, 5.13; N, 10.99

[0125]

Example 70

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one hydrochloride

A 1N solution of hydrogen chloride in ether (4 mL) was added to a solution of 2-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one (0.50 g) obtained in Example 69c) in methanol (20 mL) and the solvent was then distilled off. Acetone and ether were added to the residue. A precipitated solid was filtered to obtain the

title compound (0.51 g, 86%) as colorless powder.

NMR (200 MHz, DMSO-d_6) δ: 1.40-1.88 (4H, m), 2.54-2.65 (1H, m), 2.73-2.79(5H, m), 3.05-3.16 (1H, m), 3.63 (2H, t), 3.88-4.15 (2H, m), 4.23-4.39 (1H, m), 4.55 (2H, s), 7.49 (1H, s), 7.74 (1H, dd), 8.00 (1H, dd), 8.17-8.31 (3H, m), 8.66 (1H, s).

Elemental analysis for $C_{24}H_{25}N_4O_4SCl \cdot HCl \cdot 1.5H_2O \cdot 0.4Et_2O$

Calculated (%): C, 51.75; H, 5.60; N, 9.43

Found (%): C, 51.95; H, 5.56; N, 9.30

[0126]

Example 71

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

71a) N-(1-Benzyloxycarbonylpiperidin-4-yl)-N-(4-methylimidazole)methylamine

N-(1-Benzyloxycarbonylpiperidin-4-yl)amine (10 g), 4-methylimidazole-5-carbaldehyde (4.7 g) and acetic acid (3.0 mL) were dissolved in 1,2-dichloroethane (100 mL), sodium triacetoxyborohydride (13.6 g) was added under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction solution was poured into an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified

with a silica gel column to obtain the title compound (8.0 g, 57%) as an oil.

NMR (200 MHz, $CDCl_3$) δ: 1.23-1.38 (2H, m), 1.85-1.95 (2H, m), 2.19 (3H, s), 2.64-2.74 (1H, m), 2.83-2.95 (2H, m), 3.72 (2H, s), 4.07-4.18 (2H, m), 5.12 (2H, s), 7.28-7.37 (5H, m), 7.44 (1H, s).

71b) 2-(1-Benzyloxycarbonylpiperidin-4-yl)-7-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one

N-(1-Benzyloxycarbonylpiperidin-4-yl)-N-(4-methylimidazole)methylamine (7.0 g) obtained in Example 71a) was dissolved in dichloromethane (70 mL), and DBU (3.4 mL) and N,N'-carbonyldiimidazole (3.5 g) were added. The reaction solution was stirred overnight, poured into an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (5.1 g, 69%) as white crystals.

NMR (200 MHz, $CDCl_3$) δ: 1.63-1.76 (2H, m), 1.84-1.90 (2H, m), 2.22 (3H, s), 2.85-2.98 (2H, m), 4.09-4.36 (3H, m), 4.27 (2H, s), 5.15 (2H, s), 7.28-7.37 (5H, m), 7.85(1H, s).

71c) 2-(1-Benzyloxycarbonylpiperidin-4-yl)-1,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one

2-(1-Benzyloxycarbonylpiperidin-4-yl)-7-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one (1.5 g) obtained

in Example 71b) was dissolved in THF (40 mL) and a 1.1 M solution of lithium hexamethyldisilazane in THF (4.2 mL) was added dropwise at -78°C. The mixture was stirred at -78°C for 30 minutes. Then, methyl iodide (0.31 mL) was added at -78°C and the mixture was stirred for 30 minutes. An aqueous ammonium chloride solution was added to the reaction solution, which was then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (1.1 g, 71%) as an oil.

NMR (200 MHz, CDCl) δ: 1.54 (3H, t), 1.58-2.08 (4H, m), 2.22 (3H, s), 2.77-2.98 (2H, m), 3.75-3.92 (1H, m), 4.26-4.46 (2H, m), 4.65 (1H, q), 5.15 (2H, s), 7.37-7.40 (5H, m), 7.76 (1H, s).

71d) 3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl chloride

3-[(6-Chloro-2-naphthyl)sulfonyl]propionic acid (14.9 g), thionyl chloride (4.4 mL) and DMF (2 drops) were suspended in toluene (100 mL), and the suspension was heated to reflux for 1.5 hours. The solvent was distilled off and the residue was washed with ether and hexane to obtain the title compound (15.5 g, 98%) as a brown solid.

NMR (200 MHz, $CDCl_3$) δ: 3.35-3.44 (2H, m), 3.49-3.57 (2H, m), 7.62 (1H, dd), 7.87-8.00 (4H, m), 8.48 (1H, s).

71e) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)-1,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

2-(1-Benzyloxycarbonylpiperidin-4-yl)-1,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one (3.3 g) obtained in Example 71c) was dissolved in ethanol (50 mL) and after addition of 10%Pd/C (50% hydrous: 1.6 g), subjected to catalytic reduction overnight under hydrogen atmosphere. The reaction solution was filtered and the filtrate was concentrated. The residue was dissolved in a mixture of an aqueous sodium hydrogencarbonate solution and chloroform and 3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl chloride (0.6 g) obtained in Example 71d) was added under ice-cooling. The reaction solution was stirred at room temperature for 2 hours and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (1.2 g, 28%) as pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.54 (3H, t), 1.88-2.05 (4H, m), 2.23 (3H, s), 2.53-2.64 (1H, m), 2.87-2.95 (2H, m), 3.08-3.20 (1H, m), 3.54-3.62 (2H, m), 3.81-3.94 (2H, m), 4.62-4.72 (2H, m), 7.60 (1H, dd), 7.79 (1H, s), 7.85-7.98 (4H, m), 8.49 (1H, s).

[0127]

Example 72

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

72a) N-Tert-butoxycarbonylpiperidin-4-yl)-N-(2-methylimidazole)methyl)amine

N-Tert-butoxycarbonylpiperidin-4-yl)amine (4.8 g), 2-methylimidazole-5-carbaldehyde (3.0 g) and acetic acid (1.7 ml) were dissolved in 1,2-dichloroethane (50 mL), and sodium triacetoxyborohydride (7.7 g) was added under ice-cooling. The mixture was stirred at room temperature overnight. The reaction solution was poured into an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (8.0 g, quantitative) as a pale yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.27-1.40 (2H, m), 1.45 (9H, s), 1.85-1.90 (2H, m), 2.15 (3H, s), 2.31 (3H, s), 2.66-2.80 (3H, m), 3.71 (2H, s), 4.00-4.18 (2H, m), 6.06 (2H, brs).

72b) 2-(Tert-butoxycarbonylpiperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one

N-(Tert-butoxycarbonylpiperidin-4-yl)-N-(2-methylimide)methyl)amine (8.0 g) obtained in Example 72a) was dissolved in dichloromethane (100 mL), and DBU (3.6 mL) and N,N'-carbonyldiimidazole (3.9 g) were added. The

reaction solution was stirred overnight, poured into an aqueous potassium carbonate solution, and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (7.8 g, 97%) as a pale yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.57-1.72 (2H, m), 1.77-1.92 (2H, m), 2.15 (3H, s), 2.57 (3H, s), 2.77-2.88 (2H, m), 4.03-4.15 (2H, m), 4.20 (2H, s), 4.29 (1H, brs).

72c) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,7-dimethyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

2-(Tert-butoxycarbonylpiperidin-4-yl)-5-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazole-3-one (5.0 g) obtained in Example 72b) was dissolved in concentrated hydrochloric acid (10 ml), and the solution was stirred at room temperature for 30 minutes. The reaction solution was dissolved in chloroform (150 ml) and an aqueous saturated sodium hydrogencarbonate solution (150 ml), and 3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl chloride (4.7 g) was added. The reaction solution was stirred at room temperature for 2 hours and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (3.8

g, 50%) as a white crystal.

NMR (200 MHz, $CDCl_3$) δ: 1.62-1.79 (2H, m), 1.83-1.99 (2H, m), 2.15 (3H, s), 2.57 (3H, s), 2.64-2.71 (1H, m), 2.86-2.99 (2H, m), 3.31-3.26 (1H, m), 3.49-3.63 (2H, m), 3.97-4.18 (4H, m), 4.75-4.96 (1H, m), 7.61 (1H, dd), 7.89-7.99 (4H, m), 8.49 (1H, s).

[0128]

Example 73

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-[2-(1H-imidazol-4-yl)ethyl]piperidine

73a) 2-{1-[3-(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)ethanol

3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl chloride (7.57 g) obtained in Example 71d) was added in portions to a mixture of 2-(4-piperidinyl)ethanol (3.70 g) and sodium hydrogencarbonate (2.03 g) in water (50 mL)-THF (50 mL). The reaction solution was stirred at 0°C for 1 hour and the organic solvent was then distilled off. The residue was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a silica gel column to obtain the title compound (6.18 g, 63%) as a brown oil.

NMR (200 MHz, $CDCl_3$) δ: 1.01-1.13 (2H, m), 1.45-1.56 (2H, m), 1.67-1.81 (2H, m), 2.45-2.57 (1H, m), 2.80-2.90 (2H, m),

2.93-3.06 (1H, m), 3.52-3.60 (2H, m), 3.66-3.83 (3H, m), 4.44-4.50 (1H, m), 7.59 (1H, dd), 7.93-7.97 (4H, m), 8.47 (1H, s).

73b) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)ethyl iodide

Under ice-cooling, methanesulfonyl chloride (1.4 mL) was added to a solution of 2-{1-[3-(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)ethanol (6.18 g) obtained in Example 73a) in ethyl acetate (100 mL), and the mixture was stirred for 1.5 hours. The reaction solution was washed with water and then dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was dissolved in acetonitrile (100 mL) and sodium iodide (11.3 g) was added. The mixture was stirred at room temperature for 24 hours. The solvent was distilled off and the residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off to obtain the residue, which was purified with a silica gel column to obtain the title compound (5.58 g, 71%).

NMR (200 MHz, $CDCl_3$) δ: 0.90-1.23 (2H, m), 1.60-1.84 (5H, m), 2.46-2.58 (1H, m), 2.82-2.90 (2H, m), 2.95-3.08 (1H, m), 3.20 (2H, t, J = 6.7), 3.51-3.60 (2H, m), 3.79-3.86 (1H, m), 4.46-4.53 (1H, m), 7.60 (1H, dd), 7.92-7.97 (4H, m), 8.48

(1H, s).

73c) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-[2-(1H-imidazol-4-yl)ethyl]piperidine

Imidazole (0.1 g) and potassium carbonate (0.4 g) were dissolved in DMF (30 mL), and 2-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)ethyl iodide (0.8 g) obtained in Example 73b) was added under ice-cooling. The reaction solution was stirred at 80°C for 4 hours and the solvent was then concentrated. The residue was poured into water and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a silica gel column to obtain the title compound (0.13 g, 19%) as pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 1.01-1.18 (2H, m), 1.29-1.57 (1H, m), 1.64-1.77 (4H, m), 2.39-2.51 (1H, m), 2.80-3.01 (3H, m), 3.51-3.60 (3H, m), 3.77-3.84 (1H, m), 3.94-4.01 (2H, m), 4.44-4.51 (1H, m), 6.90 (1H, s), 7.07 (1H, s), 7.49 (1H, brs), 7.57 (1H, dd), 7.91-7.96 (4H, m), 8.47 (1H, s).

[0129]

Example 74

5-Chloro-2-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-1H-benzimidazole

74a) Allyl 3-(5-chloro-1H-benzimidazol)thiopropionate

3-(5-Chloro-1H-benzimidazole)thiopropionic acid (Indian J. Chem., 11(11), 1119-21 (1973)) (5.0 g) was dissolved in allyl alcohol (50 mL) and thionyl chloride (1.6 mL) was added. The reaction solution was refluxed for 2 hours and then concentrated. The residue was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off to obtain the title compound (5.1 g, 90%) as a yellow oil.

NMR (200 MHz, $CDCl_3$) δ: 1.72 (9H, s), 2.97 (2H, t), 3.54 (2H, t), 4.63 (2H, dd), 5.22-5.38 (2H, m), 5.86-6.04 (1H, m), 7.17-7.28 (2H, m), 7.47-7.58 (1H, m), 7.72-7.86 (1H, m)

74b) 1-Tert-butyloxycarbonyl-5-chloro-2-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}thio-1H-benzimidazole

Allyl 3-(5-chloro-1H-benzimidazole)thiopropionate (4.0 g) obtained in Example 74a) and 4-(dimethylamino)pyridine (0.1 g) were dissolved in THF (40 mL) and di-tert-butyl dicarbonate (3.4 g) was added. The mixture was stirred at room temperature for 1 hour and then concentrated. A portion (1.5 g) of the residue was dissolved in THF (40 mL) and Meldrum's acid (0.81 g) and tetrakistriphenylphosphine palladium (0.2 g) were added. The mixture was stirred at room temperature overnight. The reaction solution was

concentrated and then dissolved in a dichloromethane (30 mL). To the solution were added 4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidine (0.52 g), triethylamine (0.53 mL), HOBt (0.32 g) and WSC (0.40 g). The mixture was stirred at room temperature for 16 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (1.4 g, 68%) as pale yellow crystals.

NMR (300 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.51-1.77 (2H, m), 1.92-1.98 (6H, m), 2.63-2.75 (1H, m), 2.83-3.00 (5H, m), 3.03-3.23 (1H, m), 3.50-3.60 (2H, m), 3.79-3.85 (2H, m), 4.06-4.23 (1H, m), 4.69-4.76 (1H, m), 6.68 (1H, s), 7.17-7.25 (1H, m), 7.45-7.54 (1H, m), 7.74-7.87 (1H, m).

74c) 5-Chloro-2-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-1H-benzimidazole

1-Tert-butyloxycarbonyl-5-chloro-2-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}thio-1H-benzimidazole (0.4 g) obtained in Example 74b) was dissolved in trifluoroacetic acid (5 mL) and stirred at room temperature for 0.5 hours. After the solvent was concentrated, the residue was made alkaline

with an aqueous potassium carbonate solution and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was dissolved in chloroform (30 mL) and m-chloroperbenzoic acid (0.74 g) was added at room temperature. The reaction solution was stirred at room temperature for 3 hours and the solvent was then distilled off. The residue was purified with a silica gel column to obtain the title compound (56 mg, 16%) as pale yellow powder.

NMR (300 MHz, $CDCl_3$) δ: 1.14-1.68 (2H, m), 1.86-2.12 (6H, m), 2.57-2.78 (1H, m), 2.85-2.99 (5H, m), 3.10-3.23 (1H, m), 3.75-3.81 (2H, m), 3.94-3.99 (3H, m), 4.36-4.42 (1H, m), 6.87 (1H, s), 7.28-7.34 (1H, m), 7.63-7.69 (2H, m), 7.89-7.94 (1H, m).

[0130]

Example 75

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanone

75a) 2-(Tert-butyloxycarbonyl-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanone

A 1 M solution (22 mL) of ethylmagnesium bromide in THF was added to a solution of 4-iodo-1H-imidazole (2.1 g) and tetramethylethylenediamine (1.7 mL) in THF (15 mL) at 25°C or lower. After the reaction solution was stirred at

60°C for 1 hour, a solution of 2-(1-tert-butyloxycarbonyl-4-piperidinyl)-N-methoxy-N-methylacetamide (2.0 g) in THF (15 mL) was added at room temperature and stirred at room temperature for 16 hours. After an aqueous ammonium chloride solution was added, the reaction solution was extracted with ethyl acetate and the extract was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified with a silica gel column to obtain the title compound (41.0 g, 47%) as an oil.

NMR (200 MHz, $CDCl_3$) δ: 1.20-1.27 (2H, m), 1.47 (9H, s), 1.71-1.78 (2H, m), 2.75-2.85 (4H, m), 3.31-3.39 (1H, m), 4.07-4.13 (2H, m), 7.19 (1H, s), 7.65 (1H, s).

75b) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanone

2-(1-Tert-butyloxycarbonyl-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanone (1.0 g) obtained in Example 75a) was dissolved in trifluoroacetic acid (10 mL), de-tert-butoxycarbonylated, and then condensed with 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (1.0 g) to obtain the title compound (0.04 g, 1.4%) as pale yellow powder in a similar manner to Example 50b).

NMR (200 MHz, $CDCl_3$) δ: 1.08-1.26 (2H, m), 1.71-1.87 (2H, m), 2.10-2.32 (1H, m), 2.50-2.62 (1H, m), 2.78-2.91 (4H, m), 2.99-3.11 (1H, m), 3.54-3.61 (2H, m), 3.78-3.85 (1H, m), 4.45-4.51 (1H, m), 7.59 (1H, dd), 7.75-7.97 (4H, m),

8.47(1H, s).

[0131]

Example 76

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanol

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-1-(1H-imidazol-4-yl)ethanone (0.1 g) obtained in Example 75b) was dissolved in methanol (10 mL) and sodium borohydride (0.1 g) was added under ice-cooling. The mixture was stirred at room temperature for 2 hours. After 1N hydrochloric acid was added to the reaction solution, the solvent was concentrated. The residue was poured into an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (18 mg, 17%) as pale yellow powder.

NMR (200 MHz, $CDCl_3$) δ: 0.92-1.20 (2H, m), 1.27 (1H, s), 1.71-1.79 (5H, m), 2.41-2.58 (1H, m), 2.84-3.07 (3H, m), 3.52-3.58 (2H, m), 3.74-3.81 (1H, m), 4.38-4.45 (1H, m), 4.80-4.98 (1H, m), 7.57 (1H, dd), 7.92-7.97 (4H, m), 8.47 (1H, s).

[0132]

Example 77

1-{3-[(6-Chloro-2-napthyl)sulfonyl]propanoyl}-4-(4-methyl-1H-imidazol-5-yl)piperidine

WSC (0.45 g) was added to a solution of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.5 g), 4-(4-methyl-1H-imidazol-5-yl)piperidine dihydrochloride (Farmaco, 47(11), 1343-65(1992)) (0.63 g) and HOBt (0.36 g) in dichloromethane (30 mL) and stirred at room temperature for 16 hours. The reaction solution was made alkaline with an aqueous potassium carbonate solution and then extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified with a basic silica gel column to obtain the title compound (32 mg, 4%) as pale yellow powder. NMR (200 MHz, $CDCl_3$) δ: 1.63-1.83 (4H, m), 2.26 (3H, s), 2.54-2.66 (1H, m), 2.74-2.90 (3H, m), 3.07-3.17 (1H, m), 3.53-3.59 (2H, m), 3.89-3.93 (1H, m), 4.56-4.61 (1H, m), 6.76 (1H, s), 7.53 (1H, s), 7.58 (1H, dd), 7.89-7.96 (4H, m), 8.47 (1H, s).

[0133]

Example 78

2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-ethyl-7-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

78a) 1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(2-ethyl-4-methyl-1H-imidazol-5-yl)methyl]piperidine-4-amine

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidineamine (3.0 g) obtained in Example 50a) and 2-ethyl-4-methylimidazole-5-carbaldehyde (1.1 g), the title compound (2.0 g, 50%) was prepared as pale yellow powder by reductive amination according to a similar manner to Example 51.

NMR (200 MHz, $CDCl_3$) δ: 1.33 (3H, t), 1.48-1.72 (2H, m), 1.84-1.97 (2H, m), 2.16 (3H, s), 2.45-2.66 (1H, m), 2.82-2.97 (5H, m), 3.11-3.22 (1H, m), 3.52-3.75 (4H, m), 3.81-4.01 (1H, m), 4.11-4.45 (1H, m), 7.39 (1H, s), 7.58 (1H, dd), 7.89-7.97 (4H, m), 8.47 (1H, s).

78b) 2-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-ethyl-7-methyl-1,2-dihydro-3H-imidazo[1,5-c]imidazol-3-one

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-[(2-ethyl-4-methyl-1H-imidazol-5-yl)methyl]piperidine-4-amine (2.0 g) obtained in Example 78a), DBU (0.6 mL) and N,N'-carbonyldiimidazole (0.7 g), the title compound (71 mg, 4%) was obtained as white crystals in a similar manner to Example 65.

NMR (200 MHz, $CDCl_3$) δ: 1.33 (3H, t), 1.56-1.71 (2H, m), 1.84-1.93 (2H, m), 2.17 (3H, s), 2.58-2.66 (1H, m), 2.86-2.98 (4H, m), 3.13-3.22 (1H, m), 3.52-3.62 (2H, m), 3.97-4.01 (1H, m), 4.11-4.15 (1H, m), 4.18 (2H, s), 4.68-4.72 (1H, m), 7.58 (1H, dd), 7.89-7.96 (4H, m), 8.47 (1H, s).

[0134]

Example 79

6-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-6,7-dihydro-5H-imidazo[1,5-a]imidazol-5-one

From 1-{3-[(6-chloro-2-napthyl)sulfonyl]propanoyl}-N-(2-imidazolyl)methyl-4-piperidineamine (1.5 g) obtained in Example 54, DBU (0.16 mL) and N,N'-carbonyldiimidazole (0.19 g), the title compound (0.62 g, 19%) was obtained as pale yellow powder in a similar manner to Example 65.

NMR (200 MHz, $CDCL_3$) δ: 1.60-1.75 (2H, m), 1.90-2.05 (2H, m), 2.64 (3H,t), 2.85-3.15 (2H, m), 3.19 (3H, t), 3.49-3.70 (2H, m), 3.99-4.04 (1H, m), 4.22-4.30 (1H, m), 4.31 (2H, s), 4.70-4.75 (1H, m), 7.18 (1H, d), 7.31 (1H, d), 7.59 (1H, dd), 7.89-7.96 (4H, m), 8.48 (1H, s).

[0135]

Example 80

N-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-N-(4-methyl-1H-imidazol-5-yl)methylacrylamide

From 1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-N-(4-methyl-1-tritylimidazol-5-yl)methyl-4-piperidineamine (1.5 g) and 3-bromopropionyl chloride (0.24 mL), the title compound (0.34 g, 33%) was obtained as pale yellow powder in a similar manner to Example 55.

NMR (200 MHz, $CDCl_3$) δ: 1.61-1.89 (4H, m), 2.23 (3H, s), 2.48-2.67 (1H, m), 2.82-3.17 (3H, m), 3.57-3.64 (2H, m),

3.80-4.07 (2H, m), 4.39 (2H, s), 4.60-4.82 (1H, m), 5.78-5.82 (1H, m), 6.38 (1H, dd), 6.50-6.78 (1H, m), 7.45 (1H, s), 7.61 (1H, dd), 7.91-7.99 (4H, m), 8.50 (1H, s).

[0136]

Example 81

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-8-methylimidazo[1,2-a]pyridine hydrochloride

81a) Tert-butyl 4-(8-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecarboxylate

A solution of tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 3-methyl-2-aminopyridine (0.28 g) in ethanol (10 mL) was refluxed for 4 hours. After the reaction solution was concentrated under reduced pressure, the residue was dissolved in ethyl acetate and 1N hydrochloric acid and an aqueous layer was separated. The aqueous layer was made alkaline with 6N sodium hydroxide and extracted with ethyl acetate. The extract was washed with an aqueous saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (0.65 g, 79%) as a colorless oil.

NMR (300 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.66-1.78 (2H, m), 1.90 (1H, br), 2.09 (1H, br), 2.61 (3H, s), 2.78-2.97 (3H, m), 3.24 (1H, m), 4.25 (1H, m), 6.73 (1H, q, J = 6.9), 6.95 (1H, m), 7.39 (1H, d, J = 2.4), 7.84 (1H, dd, J = 3.0, 6.3).

81b) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-8-methylimidazo[1,2-a]pyridine hydrochloride

Concentrated hydrochloric acid (2 mL) was added to tert-butyl 4-(8-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecarboxylate (0.47 g) obtained in Example 81a), diluted with ethanol, and then concentrated under reduced pressure. The residue was suspended in acetonitrile (10 mL), and triethylamine (0.63 mL) and DBU (0.45 mL) were added. This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), WSC (0.43 g) and HOBt (0.35 g) in acetonitrile (10 mL) and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column (ethyl acetate/methanol=10/1). The resulting white powder was treated with a 4N solution of hydrogen chloride in ethyl acetate and a precipitated solid was filtered. The resulting solid was dried under reduced pressure to obtain the title compound (0.28 g, 38%) as a white solid.

NMR (200 MHz, $CDCl_3$) δ: 1.53-1.84 (2H, m), 2.05-2.20 (2H, m), 2.60 (3H, s), 2.77 (1H, m), 2.90-2.96 (2H, m), 3.05 (1H,

m), 3.26 (1H, m), 3.55-3.63 (2H, m), 4.00 (1H, d, J = 13.8), 4.62 (1H, d, J = 13.8), 6.76 (1H, t, J = 7.0), 6.97 (1H, d, J = 7.0), 7.36 (1H, s), 7.56-7.61 (1H, m), 7.82 (1H, d, J = 7.0), 7.90-7.97 (4H, m), 8.49 (1H, s).

Elementary analysis for $C_{26}H_{26}N_3O_3SCl \cdot HCl \cdot H_2O$

Calculated (%): C, 56.73; H, 5.31; N, 7.63.

Found (%): C, 57.09; H, 5.50, N, 7.32.

[0137]

Example 82

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-7-methylimidazo[1,2-a]pyridine hydrochloride

82a) Tert-butyl 4-(7-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidincarboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 4-methyl-2-aminopyridine (0.28 g), the title compound (0.65 g, 79%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.62-1.78 (2H, m), 2.04-2.08 (2H, m), 2.39 (3H, s), 2.85-2.98 (3H, m), 4.25 (2H, d, J = 14.6), 6.65 (1H, d, J = 7.4), 7.32 (1H, s), 7.37 (1H, s), 7.83 (1H, d, J = 7.4).

82b) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-7-methylimidazo[1,2-a]pyridine hydrochloride

From tert-butyl 4-(7-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecarboxylate (0.47 g) obtained in Example

82a) and 3-[6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), the title compound (0.30 g, 39%) was obtained in a similar manner to Example 81b).

NMR (300 MHz, $CDCl_3$) δ: 1.56-1.79 (2H, m), 2.06-2.18 (2H, m), 2.36 (3H, s), 2.73-2.82 (1H, m), 2.91-2.96 (2H, m), 3.00-3.09 (1H, m), 3.20-3.30 (1H, m), 3.58-3.62 (2H, m), 4.00 (1H, d, J = 14.4), 4.62 (1H, d, J = 14.4), 7.02 (1H, d, J = 7.2), 7.32 (1H, s), 7.50-7.60 (2H, m), 7.68 (1H, s), 7.86-7.96 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{26}H_{26}N_3O_3SCl \cdot HCl \cdot H_2O$

Calculated (%): C, 56.73; H, 5.31; N, 7.63.

Found (%): C, 56.95; H, 5.42, N, 7.50.

[0138]

Example 83

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-6-methylimidazo[1,2-a]pyridine hydrochloride

83a) Tert-butyl 4-(6-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecarboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 5-methyl-2-aminopyridine (0.28 g), the title compound (0.67 g, 81%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.65-1.80 (2H, m), 1.95-2.09 (2H, m), 2.35 (3H, s), 2.88-3.00 (3H, m), 4.27 (2H, d, J = 13.2), 7.00 (1H, dd, J = 1.8, 9.4), 7.35 (1H,

s), 7.52 (1H, d, J = 9.4), 7.70 (1H, d, J = 1.8).

83b) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-6-methyl[1,2-a]pyridine hydrochloride

From tert-butyl 4-(6-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecarboxylate (0.47 g) obtained in Example 83a) and 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), the title compound (0.36 g, 45%) was obtained in a similar manner to Example 81b).

NMR (200 Hz, $CDCl_3$) δ: 1.56-1.76 (2H, m), 2.11-2.18 (2H, m), 2.40 (3H, s), 2.73-2.82 (1H, m), 2.91-2.96 (2H, m), 3.00-3.09 (1H, m), 3.20-3.30 (1H, m), 3.56-3.62 (2H, m), 3.97 (1H, d, J = 14.4), 4.61 (1H, d, J = 14.4), 6.66 (1H, d, J = 7.2), 7.28 (1H, d, J = 2.7), 7.37 (1H, s), 7.57-7.60 (1H, m), 7.81 (1H, d, J = 7.2), 7.89-7.96 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{26}H_{26}N_3O_3SCl \cdot HCl \cdot H_2O$

Calculated (%) C, 56.73; H, 5.31; N, 7.63.

Found (%) C, 56.54; H, 5.44, N, 7.54.

[0139]

Example 84

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methylimidazo[1,2-a]pyridine hydrochloride

84a) Tert-butyl 4-(5-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecaroboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 6-methyl-2-aminopyridine

(0.28 g), the title compound (0.65 g, 79%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.45 (9H, m), 1.66-1.78 (2H, m), 1.88-2.05 (2H, m), 2.84 (3H, s), 2.78-2.91 (2H, m), 3.41 (1H, m), 4.27 (2H, d, J = 13.2), 6.50 (1H, d, J= 7.0), 7.02 (1H, dd, J = 7.0, 9.2), 7.45 (1H, s), 7.47 (1H, d, J = 9.2).

84b) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5-methylimidazo[1,2-a]pyridine hydrochloride

From tert-butyl 4-(5-methylimidazo[1,2-a]pyridin-3-yl)-1-piperidinecaroboxylate (0.47 g) obtained in Example 84a) and 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), the title compound (0.33 g, 41%) was obtained in a similar manner to Example 81b).

NMR (300 MHz, $CDCl_3$) δ: 1.53-1.77 (2H, m), 2.05-2.17 (2H, m), 2.65 (1H, m), 2.82 (3H, s), 2.90-2.95 (2H, m), 3.20 (1H, m), 3.44-3.62 (3H, m), 3.97 (1H, d, J = 13.5), 4.66 (1H, d, J = 13.5), 6.51 (1H, d, J = 6.9), 7.03 (1H, dd, J = 6.9, 9.0), 7.40 (1H, s), 7.47 (1H, d, J = 9.0), 7.57 (1H, dd, J = 2.1, 9.0), 7.88-7.95 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{26}H_{26}N_3O_3SCl \cdot HCl \cdot H_2O$

Calculated (%) C, 56.73; H, 5.31; N, 7.63.

Found (%) C, 56.59; H, 5.31, N, 7.30.

[0140]

Example 85

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)imidazo[1,2-a]pyrazine

85a) Tert-butyl 4-imidazo[1,2-a]pyrazin-3-yl-1-piperidinecarboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 2-aminopyrazine (0.28 g), the title compound (0.44 g, 56%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.64-1.85 (4H, m), 2.78-3.23 (3H, m), 4.30 (d, J = 13.2), 7.61 (1H, d, J = 2.2), 7.87-7.94 (2H, m), 9.09 (1H, d, J = 1.0)

85b) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)imidazo[1,2-a]pyrazine

Concentrated hydrochloric acid (2 mL) was added to tert-butyl 4-imidazo[1,2-a]pyrazin-3-yl-1-piperidinecarboxylate (0.38 g) obtained in Example 85a), diluted with ethanol, and then concentrated under reduced pressure. The residue was suspended in acetonitrile (10 mL), and triethylamine (0.63 mL) and DBU(0.45 mL) were added. This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), WSC (0.43 g) and HOBt (0.35 g) in acetonitrile (10 mL), and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The

chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column (8/1 ethyl acetate-methanol) to obtain the title compound as a colorless powdery solid (0.25 g, 36%).

NMR (200 MHz, $CDCl_3$) δ: 1.63-1.82 (2H, m), 2.05-2.21 (2H, m), 2.78 (1H, m), 2.95 (2H, t, J = 7.0), 3.09-3.35 (2H, m), 3.59 (2H, t, J = 7.0), 4.03 (1H, d, J = 14.0), 4.68 (1H, d, J = 14.0), 7.58-7.63 (2H, m), 7.91-7.96 (6H, m), 8.49 (1H, s), 9.10 (1H, s).

Elemental analysis for $C_{24}H_{23}N_4O_3SCl \cdot 0.5H_2O \cdot 0.5AcOEt$

Calculated (%) C, 58.26; H, 5.26; N, 10.45.

Found (%) C, 58.13; H, 5.29, N, 10.75.

[0141]

Example 86

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)imidazo[1,2-a]pyrimidine

86a) Tert-butyl 4-imidazo[1,2-a]pyrimidin-3-yl-1-piperidinecarboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (1.0 g) and 2-aminopyrimidine (0.25 g), the title compound (0.43 g, 55%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.65-2.07 (4H, m), 2.87-3.02 (3H, m), 4.27 (2H, d, J = 14.0), 6.90 (1H, dd, J

= 4.0, 7.0), 7.61 (1H, s), 8.30 (1H, dd, J = 2.0, 7.0), 8.55 (1H, dd, J = 2.0, 4.0)

86b) 3-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)imidazo[1,2-a]pyrimidine

From tert-butyl 4-imidazo[1,2-a]pyrimidin-3-yl-1-piperidinecarboxylate (0.35 g) obtained in Example 86a) and 3-(6-chloro-naphthalene-2-sulfonyl)propionic acid (0.38 g), the title compound (0.12 g, 20%) was obtained in a similar manner to Example 85b).

NMR (200 MHz, $CDCl_3$) δ: 1.62-1.88(2H, m), 2.00-2.18 (2H, m), 2.71-2.84 (1H, m), 2.94 (2H, t, J = 7.0), 3.06-3.20 (1H, m), 3.21-3.33 (1H, m), 3.59 (2H, t, J = 7.0), 4.03 (1H, d, J = 13.4), 4.65 (1H, d, J = 13.4), 6.91 (1H, dd, J = 4.2, 7.0), 7.57-7.62 (2H, m), 7.89-7.97 (4H, m), 8.33 (1H, dd, J = 1.8, 7.0), 8.49 (1H, s), 8.55 (1H, dd, J = 1.8, 4.2)

Elemental analysis for $C_{24}H_{23}N_4O_3SCl \cdot 1.5H_2O$

Calculated (%) C, 56.52; H, 5.14; N, 10.99.

Found (%) C, 56.77; H, 4.82; N, 10.99.

[0142]

Example 87

3-(1-{3-[(7-Chloro-2H-chromen-3-yl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine hydrochloride

87a) 3-[(7-Chloro-2H-chromen-3-yl)sulfonyl]propionic acid

3-(7-Chloro-2H-chromen-3-yl)sulfonyl chloride (5.0 g)

was added to a solution of sodium hydrogencarbonate (3.2 g) and sodium sulfite (2.6 g) in water (100 mL) and stirred at 70°C for 90 minutes. Then, sodium hydroxide (1.9 g) and bromosuccinic acid (9.3 g) were added and the mixture was stirred at 110°C for 8 hours. The reaction solution was allowed to be cooled. A precipitate was filtered, washed with water, and then concentrated under reduced pressure to obtain the title compound (4.1 g, 71%) as a light brown solid.

NMR (300 MHz, DMSO-d_6) δ: 2.63 (2H, t, J = 7.2), 3.50 (2H, t, J = 7.2), 5.62 (2H, s), 7.04-7.11 (2H, m), 7.46-7.49 (2H, m).

87b) 3-(1-{3-[(7-Chloro-2H-chromen-3-yl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine hydrochloride

A solution of 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.92 g), triethylamine (1.3 mL) and DBU (0.99 mL) in acetonitrile (10 mL) was added to a suspension of 3-[(7-chloro-2H-chromen-3-yl)sulfonyl]propionic acid (0.91 g) obtained in Example 87a), WSC (0.86 g) and HOBt (0.64 g) in acetonitrile (20 mL), and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a

chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column and the resulting pale yellow viscous substance was treated with a saturated solution of hydrogen chloride in ethanol to obtain the title compound (1.36 g, 86%).

NMR (200 MHz, $CDCl_3$) δ: 1.39-1.72 (2H, m), 1.84-2.03 (6H, m), 2.62-2.68 (2H, m), 2.83-2.89 (4H, m), 3.10-3.24 (1H, m), 3.44-3.52 (2H, m), 3.81 (2H, t, J = 6.0), 3.92 (1H, d, J = 13.8), 4.60 (1H, d, J = 13.8), 5.04 (2H, s), 6.64 (1H, s), 6.92-6.98 (2H, m), 7.10 (1H, d, J = 8.4), 7.32 (1H, s)

[0143]

Example 88

3-(1-{3-[(7-Bromo-2H-chromen-3-yl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

From 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.46 g) and 3-[(7-bromo-2H-chromen-3-yl)sulfonyl]propionic acid (0.52 g) obtained in Example 87a), the title compound (0.51 g, 58%) was obtained as a colorless solid in a similar manner to Example 87b).

NMR (300 MHz, $CDCl_3$) δ: 1.35-1.63 (2H, m), 1.85-2.02 (6H, m), 2.62-2.71 (2H, m), 2.84-2.89 (4H, m), 3.10-3.22 (1H, m), 3.45-3.51 (2H, m), 3.81 (2H, t, J = 5.7), 3.92 (1H, t, J = 14.1), 4.60 (1H, d, J = 14.1), 5.03 (2H, s), 6.64 (1H, s), 7.02-7.14 (3H, m), 7.32 (1H, s)

[0144]

Example 89

3-[1-(3-{[(E)-2-(4-chlorophenyl)vinyl]sulfonyl}propanoyl)-4-piperidinyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

89a) [(E)-2-(4-chlorophenyl)vinyl]sulfonylpropionic acid

From [(E)-2-(4-chlorophenyl)vinyl]sulfonyl chloride (30. g), the title compound (0.86 g, 25%) was obtained in a similar manner to Example 87a).

NMR (200 MHz, DMSO-d_6) δ: 2.66 (2H, t, J = 7.4), 3.41 (2H, t, J = 7.4), 7.48-7.57 (4H, m), 7.76-7.81 (2H, m).

89b) 3-[1-(3-{[(E)-2-(4-chlorophenyl)vinyl]sufonyl}propanoyl-4-piperidinyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

A solution of 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.46 g), triethylamine (0.65 mL) and DBU (0.49 mL) in acetonitrile (10 mL) was added to a suspension of 3-[(E)-2-(4-chlorophenyl)vinyl]sulfonylpropionic acid (0.41 g) obtained in Example 89a), WSC (0.43 g) and HOBt (0.32 g) in acetonitrile (20 mL) and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off.

The residue was purified with a silica gel column to obtain the title compound (0.12 g, 18%) as a colorless solid.

NMR (300 MHz, $CDCl_3$) δ: 1.39-1.68 (2H, m), 1.83-2.01(6H, m), 2.62-2.74 (2H, m), 3.83-3.92 (4H, m), 3.11-3.23 (1H, m), 3.50 (2H, t, J = 7.2), 3.80 (2H, t, J = 5.7), 3.94 (1H, d, J = 14.1), 4.61 (1H, d, J = 14.1), 6.62 (1H, s), 6.85 (1H, d, J = 15.3), 7.39-7.48 (4H, m), 7.54 (1H, d, J = 15.3).

Elemental analysis for $C_{23}H_{28}N_3O_3SCl \cdot 1.5H_2O$

Calculated (%) C, 56.49; H, 6.39; N, 8.59.

Found (%) C, 56.35; H, 6.12; N, 8.37.

[0145]

Example 90

3-[1-(3-{[(E)-2-(4-bromophenyl)vinyl]sulfonyl}propanoyl)-4-piperidinyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

90a) 3-{[(E)-2-(4-bromophenyl)vinyl]sulfonyl}propionic acid

From [(E)-2-(4-bromophenyl)vinyl]sulfonyl chloride (1.0 g), the title compound (0.31 g, 27%) was obtained in a similar manner to Example 87a).

NMR (200 MHz, DMSO-d_6) δ: 2.65 (2H, t, J = 7.4), 3.39 (2H, t, J = 7.4), 7.48-7.57 (4H, m), 7.76-7.85 (2H, m).

90b) 3-[1-(3-{[(E)-2-(4-bromophenyl)vinyl]sulfonyl}propanoyl)-4-piperidinyl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

From 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.30 g) and 3-{[(E)-2-(4-

bromophenyl)vinyl]sulfonyl}propionic acid (0.31 g) obtained in Example 90a), the title compound (0.17 g, 34%) was obtained in a similar manner to Example 89b).

NMR (300 MHz, $CDCl_3$) δ: 1.38-1.67 (2H, m), 1.88-2.00 (6H, m), 2.62-2.74 (2H, m), 2.83-2.89 (4H, m), 3.11-3.23 (1H, m), 3.50 (2H, t, J = 6.6), 3.80 (2H, t, J = 6.0), 3.93 (1, d, J = 12.6), 4.60 (1H, d, J = 12.6), 6.63 (1H, s), 6.87 (1H, d, J = 15.3), 7.37-7.59 (5H, m).

[0146]

Example 91

N-(6-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthyl)acetamide

91a) Pyridinium 6-acetylaminonapthalene-2-sulfonate

A mixture of 6-aminonaphthalene-2-sulfonic acid (11.2 g), acetic acid (23.6 mL) and pyridine (12.1 mL) was stirred at room temperature for 16 hours. Diethyl ether was added to the reaction solution and a precipitate was filtered to obtain the title compound (16.4 g, 96%) as a colorless solid.

NMR (200 MHz, DMSO-d_6) δ: 2.11 (3H, s), 7.57 (1H, dd, J = 2.2, 8.8), 7.65 (1H, dd, J = 1.5, 8.8), 7.74 (1H, d, J = 8.8), 7.65 (1H, dd, J = 1.5, 8.8), 7.74 (1H, d, J = 8.8), 7.90 (1H, d, J= 8.8), 8.02-8.09 (3H, m), 8.27 (1H, d, J = 1.5), 8.54-8.63 (1H, m), 8.91-8.95 (2H, m).

91b) 6-Acetylaminonaphthalene-2-sulfonyl chloride

Under ice-cooling, thionyl chloride (3.5 mL) was added to a solution of pyridinium 6-acetylaminonapthalene-2-sulfonate (15.0 g) obtained in Example 91a) in DMF (20 mL). The reaction solution was stirred at room temperature for 90 minutes and then poured into a mixture of ethyl acetate and iced water to separate an ethyl acetate layer. The ethyl acetate solution was washed with 1N hydrochloric acid, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified with a silica gel column to obtain the title compound (1.67 g, 14%) as a pale yellow solid.

NMR (200 MHz, $CDCl_3$) δ: 2.29 (3H, s), 7.50 (1H, dd, J = 2.2, 8.8), 7.95-7.99 (3H, m), 8.44 (1H, s), 8.51 (1H, s).

91c) 3-[(6-Acetylamino-2-naphthyl)sulfonyl]propionic acid

Using 6-aminonaphthalene-2-sulfonyl chloride (1.69 g) obtained in Example 91b), the title compound (0.68 g, 36%) was obtained in a similar manner to Example 87a).

NMR (200 MHz, DMSO-d_6) δ: 2.24 (3H, s), 2.59 (2H, t, J = 7.4), 3.66 (2H, t, J = 7.4), 8.00 (1H, dd, J = 1.8, 8.4), 8.08 (1H, dd, J = 1.8, 8.4), 8.33 (1H, d, J = 8.8), 8.44 (1H, d, J = 8.8), 8.75 (2H, d, J = 9.0).

91d) N-(6-{3-oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthyl)acetamide

From 3-[(6-acetylamino-2-naphthyl)sulfonyl]propionic acid(0.68 g) obtained in Example 91c) and 3-(4-

piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.71 g) obtained in Example 209b), the title compound (0.38 g, 35%) was obtained in a similar manner to Example 89b).

NMR (300 MHz, $CDCl_3$) δ: 1.14-1.43 (2H, m), 1.79-2.00(6H, m), 2.26 (3H, s), 2.54-2.65 (2H, m), 2.80-2.88 (4H, m), 3.07 (1H, t, J = 11.1), 3.47-3.57 (1H, m), 3.66-3.88 (4H, m), 4.47 (1H, d, J = 13.2), 6.51 (1H, s), 7.59 (1H, dd, J = 2.4, 9.0), 7.80-7.93 (3H, m), 8.36 (1H, s), 8.44 (1H, s), 8.55 (1H, br)

Elemental analysis for $C_{27}H_{32}N_4O_4S \cdot 3.5H_2O$

Calculated (%) C, 56.73; H, 6.88; N, 9.80.

Found (%) C, 56.75; H, 6.94, N, 9.80.

[0147]

Example 92

3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

92a) 2-Methyl-3-pyridin-4-yl-imidazo[1,2-a]pyridine

A solution of tributyl(4-pyridinyl)tin (5.0.g), 3-bromo-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (EP 556080 (1993)) (2.6 g), dichlorobis(triphenylphosphine)palladium(0.86 g) and lithium chloride (52 mg) in toluene (20 mL) was stirred at 100°C for 12 hours under argon atmosphere. Insoluble

substances were filtered off and the filtrate was concentrated. The residue was purified with a silica gel column to obtain the title compound (0.83 g, 32%).

NMR (300 MHz, $CDCl_3$) δ: 2.54 (3H, s), 6.81 (1H, ddd, J = 2.4, 10.5, 12.3), 7.23 (1H, m), 7.42 (2H, dd, J = 2.7, 6.9), 7.61 (1H, ddd, J = 1.5, 1.5, 11.7), 8.22 (1H, ddd, J = 1.5, 1.5, 11.7), 8.77 (2H, dd, J = 2.7, 6.9).

92b) 2-Methyl-3-piperidin-4-yl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride

Palladium-carbon (0.10 g) was added to a solution of 2-methyl-3-pyridin-4-yl-imidazo[1,2-a]pyridine (0.82 g) obtained in Example 92a) in acetic acid (100 mL) and stirred at 100°C for 8 hours under hydrogen atmosphere (10 MPa). Insoluble substances were filtered off and the filtrate was concentrated. The residue was dissolved in 1N hydrochloric acid and ethanol and the solvent was distilled off to obtain the title compound (1.02 g, 89%) as a colorless solid.

NMR (200 MHz, D_2O) δ: 1.91-2.18 (8H, m), 2.33 (3H, s), 2.94 (2H, t, J = 6.6), 3.09-3.23 (3H, m), 3.58 (2H, d, J = 12.8), 4.04 (2H, t, J = 5.8).

92c) 3-(1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

From 2-methyl-3-piperidin-4-yl-5,6,7,8-

tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.50 g) obtained in Example 92b) and 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.51 g), the title compound (0.40 g, 43%) was obtained in a similar manner to Example 87b).

NMR (200 MHz, $CDCl_3$) δ: 1.70-2.00 (8H, m), 2.18 (3H, s), 2.54 (1H, m), 2.70-3.10 (6H, m), 3.57 (2H, t, J = 6.6), 3.77 (2H, t, J = 6.0), 3.96 (1H, d, J = 12.8), 4.57 (1H, d, J = 12.8), 7.60 (1H, dd, J = 1.8, 8.8), 7.93-7.97 (4H, m), 8.49 (1H, s)

Elemental analysis for $C_{26}H_{30}N_3O_3SCl \cdot HCl \cdot H_2O$

Calculated (%) C, 56.31; H, 6.00; N, 7.58.

Found (%) C, 56.35; H, 6.37, N, 7.21.

[0148]

Example 93

3-(1-{[3-(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine hydrochloride

93a) 3-Bromo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine

N-bromosuccinimide (1.3 g) was added to a solution of 6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine (Hua, D. H. et al., J. Org. Chem., 59, 5084 (1994)) (1.0 g) in carbon tetrachloride (20 mL) and stirred for 1 hour. After an aqueous saturated sodium bicarbonate solution was added, the reaction solution was extracted with chloroform. The

extract was dried over anhydrous sodium sulfate and then concentrated. The resulting residue was purified with a silica gel column to obtain the title compound (1.29 g, 81%) as a pale yellow solid.

NMR (300 MHz, $CDCl_3$) δ: 1.66-1.90 (6H, m), 2.89-2.93 (2H,m), 3.98 (2H, t, J = 4.8), 6.80 (1H, s).

93b) 3-Pyridin-4-yl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine

From 3-bromo-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine (1.29 g) obtained in Example 93a), the title compound (0.90 g, 71%) was obtained in a similar manner to Example 82a).

NMR (200 MHz, $CDCl_3$) δ: 1.76-1.93 (6H, m), 2.99 (2H, t, J = 4.8), 3.99 (2H, t, J = 4.8), 7.01 (1H, s), 7.21 (2H, m), 8.64 (2H, m).

93c) 3-Piperidin-4-yl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine dihydrochloride

From 3-pyridin-4-yl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine (0.90 g) obtained in Example 93b), the title compound (1.19 g, 96%) was obtained in a similar manner to Example 92b).

NMR (200 MHz, D_2O) δ: 176-1.95 (8H, m), 2.24 (2H, d, J = 10.2), 3.06-3.26 (5H, m), 3.57 (2H, d, J = 13.2), 4.21 (2H, t, J = 4.8), 7.11 (1H, s).

93d) 3-(1-{[3-(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine hydrochloride

From 3-piperidin-4-yl-6,7,8,9-tetrahydro-5H-imidazo[1,2-a]azepine dihydrochloride (0.50 g) obtained in Example 93c) and 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.56 g), the title compound (0.47 g, 52%) was obtained in a similar manner to Example 87b).

NMR (200 MHz, $CDCl_3$) δ: 1.39-2.00 (10H, m), 2.61-2.69 (2H, m), 2.88-2.96 (4H, m), 3.11-3.23 (1H, m), 3.51-3.60 (2H, m), 3.81-3.84 (2H, m), 3.92 (1H, d, J = 14.4), 4.56 (1H, d, J = 14.4), 6.52 (1H, s), 7.59 (1H, m), 7.90-7.97 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{26}H_{30}N_3O_3SCl \cdot HCl \cdot 0.25H_2O$

Calculated (%) C, 53.70; H, 6.24; N, 7.23.

Found (%) C, 53.96; H, 6.44, N, 7.11.

[0149]

Example 94

3-(1-{3-[(6-Vinyl-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine

94a) Tert-butyl 3-[(6-bromo-2-naphthyl)sulfonyl]propanonate

A solution of 6-bromonaphthalene-2-sulfonyl chloride (30.6 g) in THF (200 mL) was added dropwise to a solution of sodium borohydride (7.57 g) in THF (200 mL) at room temperature. The reaction solution was stirred at 40°C for 10 hours, and ice and 6N hydrochloric acid were added to

acidify the reaction solution. After extraction with ethyl acetate, the extract was washed with an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in ethyl acetate (200 mL), and triethylamine (20.8 mL) and tert-butyl acrylate (9.5 mL) were added. The mixture was refluxed for 24 hour, diluted with ethyl acetate, washed successively with 1N hydrochloric acid, an aqueous saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (28.3 g, 71%) as a pale yellow solid.

NMR (200 MHz, $CDCl_3$) δ: 1.36 (9H, s), 2.69 (2H, t, J = 8.0), 3.46 (2H, t, J = 8.0), 7.72 (1H, dd, J = 1.8, 8.8), 7.86-7.92 (3H, m), 8.12 (1H, brs), 8.46 (1H, s).

94b) Tert-butyl 3-[(6-vinyl-2-naphthyl)sulfonyl]propanoate

A solution of tert-butyl 3-(6-bromo-2-naphthyl)sulfonylpropanoate (2.0 g) obtained in Example 94a), tributyl(vinyl)tin (2.4 g), lithium chloride (1.5 g) and dichlorobis(triphenylphosphine)palladium (0.18 g) in toluene (40 ml) was stirred at 90°C for 3 hours under argon atmosphere. Insoluble substances were filtered off and the filtrate was diluted with ethyl acetate. A 10% solution of potassium fluoride in water was added and precipitated

insoluble substances were filtered with Celite. An organic layer was separated from the filtrate, washed with an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was purified with a silica gel column to obtain the title compound (0.96 g, 55%) as a colorless solid.

NMR (300 MHz, $CDCl_3$) δ: 1.36 (9H, s), 2.69 (2H, t, J = 7.2), 3.47 (2H, t, J = 7.2), 5.46 (1H, d, J = 10.8), 5.97 (1H, d, J = 17.7), 6.90 (1H, dd, J = 10.8, 17.7), 7.76-7.87 (3H, m), 7.93-7.99 (2H, m), 8.43 (1H, d, J = 1.5).

94c) 3-(6-Vinyl-2-naphthyl)sulfonylpropanoic acid

Trifluoroacetic acid (10 mL) was added to a solution of tert-butyl 3-[(6-vinyl-2-naphthyl)sulfonyl]propanoate (0.96 g) obtained in Example 94b) in toluene (10 mL) and stirred at room temperature for 12 hours. The reaction solution was concentrated to obtain the title compound (0.67 g, 83%) as a brown solid.

NMR (200 MHz, DMSO-d_6) δ: 2.59 (2H, t, J = 7.4), 3.66 (2H, t, J = 7.4), 5.46 (1H, d, J = 10.8), 5.97 (1H, d, J = 17.7), 6.90 (1H, dd, J = 10.8, 17.7), 8.00 (1H, dd, J = 1.8, 8.4), 8.08 (1H, dd, J = 1.8, 8.4), 8.33 (1H, d, J = 8.8), 8.44 (1H, d, J = 8.8), 8.75 (2H, d, J = 9.0).

94d) 3-(1-{3-[(6-Vinyl-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine hydrochloride

From 3-(6-vinyl-2-naphthyl)sulfonylpropanoic acid (0.33 g) obtained in Example 94c) and 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.38 g)), the title compound (0.36 g, 57%) was obtained as a white solid in a similar manner to Example 87b).

NMR (200 MHz, $CDCl_3$) δ: 1.36-1.75 (2H, m), 1.87-2.04 (6H, m), 2.57-2.70 (2H, m), 2.82-2.93 (4H, m), 3.11 (1H, m), 3.53-3.61 (2H, m), 3.80 (2H, t, J = 5.8), 3.91 (1H, d, J = 13.6), 4.57 (1H, d, J = 13.6), 5.47 (1H, d, J = 11.0), 5.96 (1H, d, J = 17.6), 6.65 (1H, s), 6.90 (1H, dd, J = 11.0, 17.6), 7.75-8.01 (5H, m), 8.45(1H, s).

Elemental analysis for $C_{27}H_{31}N_3O_3S \cdot HCl \cdot 1.8H_2O$

Calculated (%) C, 59.34; H, 6.57; N, 7.69.

Found (%) C, 59.55; H, 6.96, N, 7.79.

[0150]

Example 95

3-(1-{3-[(6-Vinyl-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)imidazo[1,2-a]pyridine

From 3-(6-vinyl-2-naphthyl)sulfonylpropanoic acid (0.33 g) obtained in Example 94c) and 3-(4-piperidinyl)imidazo[1,2-a]pyridine dihydrochloride (0.37 g), the title compound (0.15 g, 26%) was obtained in a similar manner to Example 89b).

NMR (300 MHz, $CDCl_3$) δ: 1.54-1.80 (2H, m), 2.07-2.20 (2H, m), 2.77 (1H, m), 2.93 (2H, t, J = 7.5), 3.08 (1H, m), 3.26

(1H, m), 3.57-3.62 (2H, m), 3.99 (1H, d, J = 13.5), 4.62 (1H, d, J = 13.5), 5.47 (1H, d, J = 11.1), 5.97 (1H, d, J = 17.7), 6.82-6.96 (2H, m), 7.38 (1H, s), 7.61-7.65 (1H, d, J = 10.8), 7.77-8.01 (6H, m), 8.46 (1H, s).

Elemental analysis for $C_{27}H_{31}N_3O_3S \cdot HCl \cdot 2H_2O$

Calculated (%) C, 59.39; H, 5.91; N, 7.69.

Found (%) C, 59.45; H, 5.94, N, 7.56.

[0151]

Example 96

6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthonitrile

96a) Tert-butyl 3-(6-cyano-naphthalene-2-yl)sulfonylpropionate

A solution of tert-butyl 3-[(6-bromo-2-naphthyl)sulfonyl]propanoate (3.9 g) obtained in Example 94a), zinc cyanate (0.69 g) and tetrakis(triphenylphosphine)palladium (0.56 g) in DMF (40 mL) was stirred at 80°C for 5 hours under argon atmosphere. After allowed to cool, the reaction solution was poured into a mixture of ethyl acetate and water to separate an ethyl acetate layer. The ethyl acetate solution was washed with 5% aqueous ammonia and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was solidified with isopropyl ether to obtain the title compound (2.04 g, 60%) as a pale

yellow solid.

NMR (200 MHz, $CDCl_3$) δ: 1.36 (9H, s), 2.71 (2H, t, J = 7.6), 3.50 (2H, t, J = 7.6), 7.79 (1H, dd, J = 1.6, 8.4), 7.99-8.15 (3H, m), 8.35 (1H, s), 8.55 (1H, s).

96b) 3-(6-Cyano-2-naphthyl)sulfonylpropanoic acid

From tert-butyl 3-[(6-cyano-2-naphthyl)sulfonyl]propanoate (0.85 g) obtained in Example 96a), the title compound (0.70 g, 98%) was obtained in a similar manner to Example 94c).

NMR (200 MHz, DMSO-d_6) δ: 2.59 (2H, t, J = 7.4), 3.66 (2H, t, J = 7.4), 8.00 (1H, dd, J = 1.8, 8.4), 8.08 (1H, dd, J = 1.8, 8.4), 8.33 (1H, d, J = 8.8), 8.44 (1H, d, J = 8.8), 8.75 (2H, d, J = 9.0).

96c) 6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthonitrle

From 3-(6-cyano-2-naphthyl)sulfonylpropanoic acid (0.35 g) obtained in Example 96b) and 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.34 g) obtained in Example 209b), the title compound (0.42 g, 68%) was obtained in a similar manner to Example 89b).

NMR (300 MHz, $CDCl_3$) δ: 1.35-1.75 (2H, m), 1.80-2.00 (6H, m), 2.55-2.63 (2H, m), 2.83-2.91 (4H, m), 3.10 (1H, m), 3.56 (1H, m), 3.70 (1H, m), 3.78 (2H, t, J = 5.7), 3.86 (1H,

d, J = 12.9), 4.47 (1H, d, J = 12.9), 6.50 (1H, s), 7.95-8.14 (4H, m), 8.43 (1H, s), 8.54 (1H, s).

[0152]

Example 97

6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthamide

97a) Tert-butyl 3-(6-carbamoylnaphthalene-2-sulfonyl)propanoate

Hydrogen peroxide (4 mL) and potassium carbonate (0.7 g) were added to a solution of tert-butyl 3-(6-cyano-2-naphthyl)sulfonylpropanoate (1.1 g) obtained in Example 96a) in DMSO (20 mL) and stirred at room temperature for 20 minutes. The reaction solution was diluted with ethyl acetate and water to separate an organic layer. The ethyl acetate solution was washed with an aqueous saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (0.88 g, 76%) as a colorless solid.

NMR (200 MHz, $CDCl_3$) δ: 1.36 (9H, s), 2.70 (2H, t, J = 7.0), 3.48 (2H, t, J = 7.0), 6.20 (1H, br), 6.55 (1H, br), 7.91 (1H, dd, J = 1.8, 8.8), 8.02-8.10 (3H, m), 8.42 (1H, s), 8.47 (1H, br).

97b) 3-(6-Carbamoylnaphthalene-2-sulfonyl)propanoic acid

From tert-butyl 3-(6-carbamoyl-2-naphthyl)sulfonylpropanoate (0.85 g) obtained in Example

97a), the title compound (0.73 g, quantitative) was obtained in a similar manner to Example 94c).

NMR (200 MHz, DMSO-d_6) δ: 2.59 (2H, t, J = 7.0), 3.63 (2H, t, J = 7.0), 7.64 (1H, br), 7.97 (1H, dd, J = 1.8, 8.4), 8.11 (1H, dd, J = 1.8, 8.4), 8.26-8.32 (3H, m), 8.63 (2H, br).

97c) 6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthamide

From 3-(6-carbamoyl-2-naphthyl)sulfonylpropanoic acid (0.35 g) obtained in Example 97b) and 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.32 g), the title compound (0.41 g, 73%) was obtained in a similar manner to Example 89b).

NMR (300 MHz, $CDCl_3$) δ: 1.38-1.67 (2H, m), 1.88-2.05 (6H, m), 2.61-2.71 (2H, m), 2.84-2.97 (4H, m), 3.15 (1H, m), 3.57-3.62 (2H, m), 3.81 (2H, t, J = 5.7), 3.93 (1H, d, J = 14.1), 4.55 (1H, d, J = 14.1), 6.56 (1H, s), 7.79 (1H, dd, J = 1.2, 8.4), 8.02-8.13 (3H, m), 8.34 (1H, s), 8.56 (1H, s).

Elemental analysis for $C_{26}H_{30}N_4O_4S \cdot H_2O \cdot 0.1i\text{-}Pr_2O$

Calculated (%) C, 61.11; H, 6.44; N, 10.72.

Found (%) C, 61.33; H, 6.28, N, 10.56.

[0153]

Example 98

3-(1-{3-[(6-Ethyl-2-naphthyl)sulfonyl]propanoyl}-4-

piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine hydrochloride

A solution of 3-(1-{3-[(6-ethenyl-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine hydrochloride (0.2 g) obtained in Example 94d) and palladium-carbon (0.04 g) in methanol (4 mL) was stirred for 1 hour under hydrogen atmosphere. Insoluble substances were filtered off and the filtrate was concentrated to obtain the title compound (0.2 g, 99%).

NMR (300 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.8), 1.42-1.63 (2H, m), 1.88-1.99 (6H, m), 2.60-2.69 (2H, m), 2.83-2.91 (6H, m), 3.12 (1H, m), 3.53-3.59 (2H, m), 3.80 (2H, t, J = 6.0), 3.91 (1H, d, J = 13.2), 4.56 (1H,d, J = 13.2), 6.65 (1H, s), 7.51 (1H, dd, J = 1.8, 8.7), 7.73 (1H, s), 7.83-7.97 (3H, m), 8.45 (1H, s).

Elemental analysis for $C_{27}H_{33}N_3O_3SHCl \cdot 1.25H_2O$

Calculated (%) C, 60.21; H, 6.83; N, 7.80.

Found (%) C, 60.29; H, 6.77, N, 7.53.

[0154]

Example 99

7-Acetyl-3-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

99a) Tert-butyl 4-(7-acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)-1-piperidinecarboxylate

A solution of tert-butyl 4-(imidazo[1,2-a]pyrazin-3-yl)-1-piperidinecarboxylate (1.0 g) obtained in Example 85a), acetic anhydride (1.0 mL) and palladium-carbon (0.2 g) in ethyl acetate (5 mL) was stirred at room temperature for 3 hours under hydrogen atmosphere. Insoluble substances were filtered off and the filtrate was concentrated. The residue was purified with a silica gel column to obtain the title compound (0.47 g, 41%) as a pale yellow solid.

NMR (300 MHz, $CDCl_3$) δ: 1.48 (9H, s), 1.51-1.89 (4H, m), 2.19 (3H, s), 2.59 (1H, m), 2.76-2.85 (2H, m), 3.87 (2H, t, J = 5.4), 4.04 (2H, t, J = 5.4), 4.18-4.22 (2H, m), 4.74 (2H, s), 6.76 (1H, s).

99b) 7-Acetyl-3-(1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

Trifluoroacetic acid (5 mL) was added to a solution of tert-butyl 4-(7-acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)-1-piperidinecarboxylate (0.45 g) obtained in Example 99a) in toluene 5 mL) and stirred at room temperature for 2 hours. The reaction solution was concentrated and the residue was dissolved in acetonitrile. After DBU (0.41 g) and triethylamine (0.56 mL) were added, this solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), WSC (0.43 g) and

HOBt (0.35 g) in acetonitrile (10 mL) and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (0.39 g, 54%) as a white powdery solid.

NMR (300 MHz, $CDCl_3$) δ: 1.45-1.65 (2H, m), 1.88-2.00 (2H, m), 2.19 (3H, s), 2.61-2.78 (3H, m), 2.91 (2H, t, J = 8.4), 3.15 (1H, t, J = 14.4), 3.56 (2H, t, J = 8.4), 3.84-4.10 (4H, m), 4.58 (1H, d, J = 13.5), 4.75 (2H, s), 6.74 (1H, s), 7.59 (1H, dd, J = 1.2, 8.7), 7.90-7.96 (4H, m), 8.48 (1H, s).

[0155]

Example 100

(6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthyl)methylamine dihydrochloride

100a) Tert-butyl 3-[(6-formyl-2-naphthyl)sulfonyl]propanoate

Osmium oxide (10% enmicrocapsulated, 1.1 g) was added to a solution of tert-butyl 3-[(6-vinyl-2-naphthyl)sulfonyl]propanoate (5.5 g) obtained in Example

94b) and sodium periodate (13.8 g) in acetonirile-acetone-water (1:1:1, 300 mL) and stirred at room temperature for 2 days. Insoluble substances were filtered off and the organic solvent was distilled off from the filtrate under reduced pressure. The residue was extracted with ethyl acetate and the extract was washed with an aqueous saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was purified with a silica gel column to obtain the title compound (2.56 g, 46%) as a pale yellow solid.

NMR (300 MHz $CDCl_3$) δ: 0.36 (9H, s), 2.72 (2H, t, J = 8.0), 3.50 (2H, t, J = 8.0), 8.00 (1H, dd, J = 1.2, 8.8), 8.12-8.23 (3H, m), 8.45 (1H, s), 8.55 (1H, s), 10.24 (1H, s).

100b) Tert-butyl 3-(6-hydroxymethyl-2-naphthyl)sulfonylpropanoate

Sodium borohydride (0.46 g) was added to a solution of tert-butyl 3-[(6-formyl-2-naphthyl)sulfonyl]propanoate (2.0 g) obtained in Example 100a) in ethanol and stirred at room temperature for 30 minutes. The reaction solution was concentrated and after ethyl acetate was added, the residue was washed successively with 1N hydrochloric acid, an aqueous saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution, and then dried

over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (2.0 g, 99%) as a colorless solid.

NMR (200 MHz, $CDCl_3$) δ: 1.36 (9H, s), 2.12 (1H, t, J = 5.8), 2.67 (2H, t, J =7.8), 3.45 (2H, t, J = 7.8), 4.92 (2H, d, J = 5.8), 7.61 (1H, dd, J = 1.8, 8.8), 7.83 (1H, dd, J = 1.8, 8.8), 7.91-7.98 (3H, m), 8.42 (1H, s).

100c) Tert-butyl 3-(6-azido-2-naphthyl)sulfonylpropanoate

Methanesulfonyl chloride (0.15 mL) was added to a solution of tert-butyl 3-(6-hydroxymethyl-2-naphthyl)sulfonylpropanoate (0.46 g) obtained in Example 100b) and pyridine (0.30 mL) in dichloromethane (10 mL) under ice-cooling. After stirring for 2 hours, ice was added to the reaction solution and the mixture was diluted with ethyl acetate and water. An organic layer was separated and washed successively with an aqueous saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution, dried over anhydrous sodium sulfate, and then concentrated. The residue was dissolved in acetone (10 mL) and lithium bromide (1.0 g) was added. After stirring for 3 hours, the mixture was diluted with ethyl acetate and water. An organic layer was separated, washed successively with an aqueous saturated sodium hydrogencarbonate solution and an aqueous sodium saturated chloride solution, dried over anhydrous sodium sulfate, and

then concentrated. The residue was dissolved in DMF (10 mL) and sodium azide (0.19 g) was added. After stirring for 12 hours, the reaction solution was diluted with ethyl acetate and water. An organic layer was separated, washed successively with an aqueous saturated sodium hydrogencarbonate solution and an aqueous sodium saturated chloride solution and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (0.32 g, 73%) as a colorless powdery solid.

NMR (200 MHz, $CDCl_3$) δ: 0.35 (9H, s), 2.69 (2H, t, J = 7.8), 3.47 (2H, t, J = 7.8), 4.59 (2H, s), 7.61 (1H, d, J = 1.4), 7.90 (2H, dd, J = 1.4, 8.8), 8.01-8.06 (2H, m), 8.49 (1H, br).

100d) 3-[(6-Azido-2-naphthyl)sulfonyl]propanoic acid

A solution of tert-butyl 3-(6-azido-2-naphthyl)solfonylpropionate (0.24 g) obtained in Example 100c) in formic acid (5 mL) was stirred at room temperature for 2 hours. The reaction solution was concentrated to obtain the title compound (0.22 g, 99%) as a white solid.

NMR (200 MHz, DMSO-d_6) δ: 2.57 (2H, t, J = 7.8), 3.61 (2H, t, J = 7.8), 4.73 (2H, s), 7.69 (1H, dd, J = 1.8, 8.4), 7.92 (1H, dd, J = 1.8, 8.8), 8.09 (1H, s), 8.19-8.29 (2H, m), 8.59 (1H, s).

100e) 3-(1-{3-[(6-Azido-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimodazo[1,2-a]pyridine

From 3-[(6-azido-2-naphthyl)sulfonyl]propanoic acid (0.22 g) obtained in Example100d) and 3-(4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine dihydrochloride (0.23 g) obtained in Example 209b), the title compound (0.26 g, 74%) was obtained in a similar manner to Example 89b).

NMR (200 MHz, $CDCl_3$) δ: 1.40-1.72 (2H, m), 1.82-2.05 (6H, m), 2.65 (1H, m), 2.83-2.94 (3H, m), 3.07-3.30 (3H, m), 3.53-3.61 (2H, m), 3.81 (2H, t, J = 5.8), 3.91 (1H, d, J = 13.4), 4.56 (1H, d, J = 13.4), 5.32 (2H, s), 6.65 (1H, s), 7.61 (1H, dd, J = 2.2, 8.8), 7.88-8.05 (4H, m), 8.50 (1H, s).

100f) (6-{3-Oxo-3-[4-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1-piperidinyl]propyl}sulfonyl-2-naphthyl)methylamine dihydrochloride

A solution of 3-(1-{3-[(6-azido-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (0.25 g) obtained in Example 100e) and palladium-carbon (0.05 g) in methanol (5 mL) was stirred for 2 hours under hydrogen atmosphere. Insoluble substances were filtered off and the filtrate was concentrated. The residue was purified with a silica gel column and then treated with a saturated solution of hydrogen chloride in ethanol to obtain the title compound (0.27 g, quantitative).

NMR (200 MHz, DMSO-d_6) δ: 1.26 (1H, m), 1.44 (1H, m), 1.81-1.98 (6H, m), 2.58 (1H, m), 2.76 (2H, t, J = 6.9), 2.93-2.97 (3H, m), 3.08 (1H, t, J = 14.2), 3.88 (1H, d, J = 14.2), 4.03-4.07 (2H, m), 4.25-4.34 (3H, m), 7.33 (1H, s), 7.84 (1H, dd, J = 1.5, 8.7), 7.97 (1H, dd, J = 1.8, 8.7), 8.16-8.19 (2H, m), 8.27 (1H, d, J = 7.8), 8.63 (1H, s)

[0156]

Example 101

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[(2-methyl-1H-imidazol-1-yl)methyl]piperidine hydrochloride

101a) Tert-butyl 4-(2-methyl-1H-imidazol-1-yl)methyl-1-piperidinecarboxylate

Sodium hydride (60% in oil: 0.87 g) was added to a solution of 2-methylimidazole (1.8 g) and tert-butyl 4-bromomethyl-1-piperidinecarboxylate (DeVita, Robert, J. et al., Bioorg. Med. Chem. Lett., 9, 261 (1999)) (8.5 g) in DMF (100 mL) and stirred at 80°C for 12 hours. The reaction solution was concentrated, and the residue was dissolved in chloroform, washed with an aqueous potassium carbonate solution, dried over anhydrous sodium sulfate, and then concentrated. The residue was purified with a silica gel column to obtain the title compound (0.43 g, 7%) as a light brown oil.

NMR (300 MHz, $CDCl_3$) δ: 1.13-1.28 (2H, m), 1.46 (9H, s), 1.57-1.63 (4H, m), 1.82 (1H, m), 2.37 (3H, s), 2.65 (2H, t,

J = 12.9), 3.71 (2H, d, J = 7.5), 4.16 (2H, brs), 6.78 (1H, d, J = 1.5), 6.91 (1H, d, J = 1.5).

101b) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[(2-methyl-1H-imidazol-1-yl)methyl]piperidine hydrochloride

From tert-butyl 4-(2-methyl-1H-imidazol-1-yl)methyl-1-piperidinecarboxylate (0.42 g) obtained in Example101a) and 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.45 g), the title compound (0.55 g, 74%)was obtained as a colorless solid in a similar manner to Example 81b).

NMR (200 MHz, $CDCl_3$) δ: 1.00-1.24 (2H, m), 1.48 (1H, m),1.63-1.77 (4H, m), 2.37 (3H, s), 2.49 (1H, t, J = 13.2), 2.83-2.90 (2H, m), 2.98 (1H, t, J = 13.2), 3.47-3.60 (2H, m), 3.80-3.88 (3H, m), 4.49 (1H, d, J = 11.4), 6.79 (1H, s), 6.91 (1H, s), 7.59 (1H, dd, J = 1.8, 9.0), 7.90-7.96 (4H, m), 8.47 (1H, s)

[0157]

Example102

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2-methyl-1H-imdazol-1-yl)ethyl]piperidine hydrochloride

102a) Tert-butyl 4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]piperidine-1-carboxylate

From tert-butyl 4-(2-bromoethyl)-1-piperidinecarboxylate (Dereck, B. et al., J. Med. Chem., 42, 4584 (1999)) (6.46 g) and 2-methylimidazole (0.93 g), the title compound (5.45 g, 80%) was obtained as a brown oil in

a similar manner to Example 101a).

NMR (300 MHz, $CDCl_3$) δ: 1.13-1.28 (2H, m), 1.46 (9H, s), 1.57-1.63 (4H, m), 1.82 (1H, m), 2.37 (3H, s), 2.65 (2H, t, J = 12.9), 3.71 (2H, d, J = 7.5), 4.16 (2H, brs), 6.78 (1H, d, J = 1.5), 6.91 (1H, d, J = 1.5).

102b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]piperidine

From tert-butyl 4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.43 g) obtained in Example 101a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.45 g), the title compound (0.52 g, 69%) was obtained as a colorless solid in a similar manner to Example 81b).

NMR (200 MHz, $CDCl_3$) δ: 1.00-1.24 (2H, m), 1.48 (1H, m), 1.63-1.77 (4H, m), 2.37 (3H, s), 2.49 (1H, t, J = 13.2), 2.83-2.90 (2H, m), 2.98 (1H, t, J = 13.2), 3.47-3.60 (2H, m), 3.80-3.88 (3H, m), 4.49 (1H, d, J = 11.4), 6.79 (1H, s), 6.91 (1H, s), 7.59 (1H, dd, J = 1.8, 9.0), 7.90-7.96 (4H, m), 8.47 (1H, s).

Elemental analysis for $C_{24}H_{28}N_3O_3SCl \cdot HCl \cdot 0.25H_2O$

Calculated (%): C, 55.97; H, 5.77; N, 8.16.

Found (%): C, 55.98; H, 5.74; N, 8.16.

[0158]

Example 103

5-Chloro-2-(3-{4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]-1-

piperidinyl}-3-oxopropyl)sulfonyl-1H-indole

103a) Tert-butyl 5-chloro-2-(3-{4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole-1-carboxylate

From tert-butyl 4-(2-methyl-1H-imidazol-1-yl)ethyl-1-piperidinecarboxylate (0.59 g) obtained in Example 102a) and 3-(1-tert-butoxycarbonyl-5-chloro-1H-indol-2-yl)sulfonylpropanoic acid (0.78 g) obtained in Example 211d), the title compound (0.64 g, 57%) was obtained in a similar manner to Example 85b).

NMR (200 MHz, $CDCl_3$) δ: 1.00-1.05 (2H, m), 1.53 (1H, m), 1.62-1.75 (4H, m), 1.73 (9H, m), 2.37 (3H, s), 2.50 (1H, t, J = 13.2), 2.87-3.04 (3H, m), 3.82-3.90 (3H, m), 4.00-4.08 (2H, m), 4.51 (1H, d, J = 12.8), 6.79 (1H, d, J = 1.0), 6.91 (1H, d, J = 1.0), 7.45 (1H, dd, J = 1.8, 8.8), 7.50 (1H, s), 7.65 (1H, d, J = 1.8) 7.99 (1H, d, J = 8.8).

103b) 5-chloro-2-(3-{4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole

Trifluoroacetic acid (10 mL) was added to a solution of tert-butyl 5-chloro-2-(3-{4-[2-(2-methyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole-1-carboxylate (0.50 g) obtained in Example 103a) in dichloromethane (10 mL) and stirred at room temperature for 2 hours. The reaction solution was made alkaline with potassium carbonate and then extracted with chloroform.

The extract was dried over anhydrous sodium sulfate and the solvent was distilled off to obtain the title compound (0.37 g, 90%).

NMR (200 MHz, DMSO-d_6) δ: 0.74-0.84 (2H, m), 1.38-1.75 (5H, m), 2.27 (3H, s), 2.40 (1H, t, J = 11.8), 2.70 (2H, t, J = 7.4), 2.89 (1H, t, J = 11.8), 3.57-3.70 (3H, m), 3.86 (2H, t, J = 7.4), 4.15 (1H, d, J = 11.8), 6.74 (1H, s,), 7.05 (1H, s), 7.14 (1H, s), 7.32 (1H, dd, J = 2.0, 9.0), 7.50 (1H, d, J = 9.0), 7.79 (1H, d, J = 2.0).

[0159]

Example 104

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-[3-(2-methyl-1H-imidazol-1-yl)propyl]piperidine hydrochloride

104a) Tert-butyl 4-[3-(2-methyl-1H-imidazol-1-yl)propyl]-1-piperidinecarboxylate

From tert-butyl 4-(3-bromopropyl)-1-piperidinecarboxylate (Siegel, M. G. et al., Tetrahedron, 55, 11619 (1999)) (2.0 g) and 2-methylimidazole (0.56 g), the title compound (2.05 g, quantitative) was obtained as a light brown oil in a similar manner to Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.03-1.35 (4H, m), 1.45 (9H, s), 1.59-1.82 (5H, m), 2.37 (3H, s), 2.66 (2H, t, J = 12.4), 3.81 (2H, t, J = 7.0), 4.06 (2H, br), 6.80 (1H, d, J = 1.4), 6.90 (1H, d, J = 1.4).

104b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl}-4-[3-(2-

methyl-1H-imidazol-1-yl)propyl]piperidine hydrochloride

From tert-butyl 4-[3-(2-methyl-1H-imidazol-1-yl)propyl]-1-piperidinecarboxylate (0.61 g) obtained in Example 104a) and 3-[(6-chloro-2-naphthyl)sulfonylpropionic acid (0.60 g), the title compound (0.56 g, 53%) was obtained in a similar manner to Example 81b).

NMR (300 MHz, $CDCl_3$) δ: 1.00-1.31 (4H, m), 1.52 (1H, m), 1.65-1.88 (4H, m), 2.37 (3H, s), 2.49 (1H, t, J = 11.1), 2.83-2.90 (2H, m), 3.00 (1H, t, J = 11.1), 3.47-3.58 (2H, m), 3.84 (1H, d, J= 14.1), 4.02 (2H, t, J = 6.9), 4.51 (1H, d, J = 14.1), 7.05 (1H, s), 7.05 (1H, s), 7.28 (1H, s), 7.61 (1H, dd, J = 2.1, 9.0), 7.89-7.97 (4H, m), 8.47 (1H, s).

[0160]

Example 105

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[3-(2-ethyl-1H-imidazol-1-yl)propyl]piperidine hydrochloride

105a) Tert-butyl 4-[3-(2-ethyl-1H-imidazol-1-yl)propyl]-1-piperidinecarboxylate

From tert-butyl 4-(3-bromopropyl)-1-piperidinecarboxylate (2.0 g) and 2-ethylimidazole (0.66 g), the title compound (2.06 g, 98%) was obtained as a light brown oil in a similar manner to Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.03-1.38 (6H, m), 1.45 (9H, s), 1.60-1.82 (3H, s), 2.61-2.72 (4H, m), 3.82 (2H, t, J = 7.0),

4.07 (2H, br), 6.80 (1H, d, J = 1.4), 6.94 (1H, d, J = 1.4).

105b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[3-(2-ethyl-1H-imidazol-1-yl)propyl]piperidine hydrochloride

From tert-butyl 4-[3-(2-ethyl-1H-imidazol-1-yl)propyl]-1-piperidinecarboxylate (0.61 g) obtained in Example 105a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.60 g), the title compound (0.50 g, 46%) was obtained in a similar manner to Example 81b).

NMR (300 MHz, $CDCl_3$) δ: 0.95-1.25 (2H, m), 1.20-1.27 (2H, m), 1.34 (3H, t, J = 7.5), 1.43 (1H, m), 1.64-1.76 (4H, m), 2.47 (1H, t, J = 13.2), 2.65 (2H, q, J = 7.5), 2.83-2.88 (2H, m), 2.97 (1H, t, J = 13.2), 3.52-3.58 (2H, m), 3.82 (2H, t, J = 7.2), 4.47 (1H, d, J = 13.5), 6.79 (1H, d, J = 1.0), 6.94 (1H, J = 1.0), 7.59 (1H, dd, J = 2.4, 8.7), 7.89-7.96 (4H, m), 8.47 (1H, s).

[0161]

Example 106

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]piperidine hydrochloride

106a) Tert-butyl 4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]piperidine-1-carboxylate

From tert-butyl 4-(2-bromoethyl)-1-piperidinecarboxylate (3.0 g) obtained in Example 106a) and 2-ethylimdazole (1.0 g), the title compound (1.55 g, 52%) was obtained as a light brown oil in a similar manner to

Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.18-1.38 (7H, m), 1.46 (9H, s), 1.63-1.74 (3H, m), 2.61-2.88 (4H, m), 3.87 (2H, t, J = 7.8), 4.08 (2H, d, J = 14.2), 6.80 (1H, d, J = 1.0), 6.94 (1H, d, J = 1.0).

106b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]piperidine hydrochloride

From tert-butyl 4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.58 g) obtained in Example 106a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.66 g), the title compound (0.29 g, 28%) was obtained in a similar manner to Example 81b).

NMR (300 MHz $CDCl_3$) δ: 1.02-1.27 (2H. m), 1.35 (3H, t, J = 7.2), 1.50 (1H, m), 1.64-1.84 (4H, m), 2.49 (1H, t, J = 10.8), 2.68 (2H, q, J = 7.2), 2.84-2.90 (2H, m), 2.99 (1H, t, J = 10.8), 3.50-3.59 (2H, m), 3.81-3.89 (3H, m), 4.50 (1H, J = 13.5), 6.79 (1H, d, J = 1.2), 6.95 (1H, d, J = 1.2), 7.59 (1H, dd, J = 1.5, 9.3), 7.89-7.94 (4H, m), 8.48 (1H, s).

[0162]

Example 107

5-Chloro-2-(3-{4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole

107a) Tert-butyl 5-chloro-2-(3-{4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole-

1-carboxylate

From tert-butyl 4-(2-ethyl-1H-imidazol-1-yl)methyl-1-piperidinecarboxylate (0.58 g) obtained in Example 106a) and 3-[(1-tert-butoxycarbonyl-5-chloro-1H-indol-2-yl)sulfonyl]propionic acid (0.85 g), the title compound (0.62 g, 54%) was obtained in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 1.05-1.21 (2H, m), 1.35 (3H, t, J = 7.5), 1.52 (1H, m), 1.53-1.73 (4H, m), 1.73 (9H, s), 2.49 (1H, t, J = 9.9), 2.65 (2H, q, J = 7.5), 2.88-3.03 (3H, m), 3.81-3.89 (3H, m), 4.02-4.08 (2H, m), 4.51 (1H, d, J = 13.2), 6.79 (1H, s), 6.95 (1H, s) 7.43-7.53 (2H, m), 7.63 (1H, m), 8.98 (1H, d, J = 9.0).

107b) 5-Chloro-2-(3-{4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole

From tert-butyl 5-chloro-2-(3-{4-[2-(2-ethyl-1H-imidazol-1-yl)ethyl]-1-piperidinyl}-3-oxopropyl)sulfonyl-1H-indole-1-carboxylate (0.60 g) obtained Example 107a), the title compound (0.45 g, 91%) was obtained in a similar manner to Example 103b).

NMR (200 MHz, DMSO-d_6) δ: 0.75-0.85 (2H, m), 1.19 (3H, t, J = 7.4), 1.49-1.62 (5H, m), 2.40 (1H, t, J = 11.8), 2.48-2.52 (2H, m), 2.57 (2H, q, J = 7.4), 2.70 (2H, t, J = 7.0), 2.89 (1H, t, J = 11.8), 3.57-3.76 (3H, m), 3.85 (2H, t, J = 7.0), 4.16 (1H, d, J = 11.8), 6.73 (1H, d, J = 1.4), 7.02

(1H, d, J = 1.4), 7.14 (1H, s), 7.32 (1H, dd, J = 1.8, 8.8), 7.51 (1H, d, J = 8.8), 7.90 (1H, d, J = 1.8).

[0163]

Example 108

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(4,5-dimethyl-1H-imidazol-1-yl)ethyl]piperidine

108a) Tert-butyl 4-[2-(4,5-dimethyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate

From 4,5-dimethylimidazole (JP-A 60-56961)(0.66 g) and tert-butyl 4-(2-bromoethyl)piperidine-1-carboxylate (2.0 g), the title compound (0.38 g, 18%) was obtained as a dark brown oil in a similar manner to Example 101a).

NMR (300 MHz, $CDCl_3$) δ: 1.07-1.91 (2H, m), 1.45 (9H, s), 1.59-1.70 (5H, m), 2.11 (3H, s), 2.15 (3H, s), 2.67 (2H, t, J = 11.4), 3.81 (2H, t, J = 7.0), 4.07-4.14 (2H, m), 7.30 (1H, s).

108b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(4,5-dimethyl-1H-imidazol-1-yl)ethyl]piperidine

From tert-butyl 4-[2-(4,5-dimethyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.38 g) obtained in Example 108a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.37 g), the title compound (0.36 g,57%) was obtained in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 1.04-1.23 (2H, m), 1.48 (1H, m), 1.60-1.77 (4H, m), 2.11 (3H, s), 2.15 (3H, s), 2.49 (1H, t,

J = 13.2), 2.83-2.90 (2H, m), 2.99 (1H, t, J = 13.2), 3.50-3.58 (2H, m), 3.79-3.84 (3H, m), 4.49 (1H, d, J = 13.2), 7.30 (1H, s), 7.59 (1H, dd, J = 2.4, 9.0), 7.89-7.94 (4H, m), 8.47 (1H, s).

Elemental analysis for $C_{25}H_{30}N_3O_3SCl \cdot 0.5H_2O$

Calculated (%) C, 60.41; H, 6.29; N, 8.45.

Found (%) C, 60.40; H, 6.42; N, 8.22

[0164]

Example 109

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2,4,5-trimethyl-1H-imidazol-1-yl)ethyl]piperidine

109a) Tert-butyl 4-[2-(2,4,5-trimethyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate

From 2,4,5-trimethylimidazole (JP-A 60-56961)(1.8 g) and tert-butyl 4-(2-bromoethyl)-1-piperidinecarboxylate (4.77 g), the title compound (1.18 g, 23%) was obtained as a dark brown oil in a similar manner to Example 101a).

NMR (300 MHz, $CDCl_3$) δ: 1.07-1.91 (2H, m), 1.46 (9H, s), 1.59-1.70 (5H, m), 2.08 (3H, s), 2.11 (3H, s), 2.15 (3H, s), 2.69 (2H, t, J = 11.4), 3.72 (2H, t, J = 7.0), 4.07-4.14 (2H, m).

109b) 1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2,4,5-trimethyl-1H-imidazol-1-yl)ethyl]piperidine

From tert-butyl 4-[2-(2,4,5-trimethyl-1H-imidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.73 g) obtained in

Example 109a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.70 g), the title compound (0.39 g, 33%) was obtained in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 1.07-1.23 (2H, m), 1.51-1.55 (3H, m), 1.70-1.79 (2H, m), 2.07 (3H, s), 2.09 (3H, s), 2.31 (3H, s), 2.51 (1H, t, J = 12.6), 2.84-2.90 (2H, m), 2.97 (1H, t, J = 12.6), 3.50-3.57 (2H, m), 3.71 (2H, t, J = 7.8), 3.83 (1H, d, J = 13.2), 7.59 (1H, dd, J = 2.1, 9.0), 7.88-7.96 (4H, m), 8.47 (1H, s).

[0165]

Example 110

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-(2-methyl-1H-imidazol-4-yl)methoxypiperidine

110a) Tert-butyl 4-(2-methyl-1-trityl-1H-imidazol-4-yl)methoxy-1-piperidinecarboxylate

Sodium hydride (60% in oil: 0.12 g) was added to a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (0.50 g) in DMF (20 mL) and stirred for 15 minutes. To the mixture, a solution of 4-chloromethyl-2-methyl-1-trityl-1H-imidazole (Cordi, A. A. et al., Eur. J. Med. Chem., 25, 557 (1990)) (0.93 g) in DMF (10 mL) was then added and was stirred for 12 hours. The reaction solution was then concentrated. The residue was dissolved in ethyl acetate, washed with an aqueous saturated sodium chloride solution, and then dried over anhydrous sulfate. The solvent was

distilled off. The residue was purified with a silica gel column to obtain the title compound (0.58 g, 53%).

NMR (200 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.45-1.63 (2H, m), 1.72 (3H, s), 1.83-1.91 (2H, m), 2.92-3.05 (2H, m), 3.58 (1H, m), 3.79-3.90 (2H, m), 4.02 (2H, s), 6.68 (1H, s), 7.10-7.17 (6H, m), 7.26-7.39 (9H, m).

110b) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-(2-methyl-1H-imidazol-4-yl)methoxypiperidine

A solution of tert-butyl 4-(2-methyl-1-trityl-1H-imidazol-4-yl)methoxy-1-piperidinecarboxylate (0.57 g) obtained in Example 110a) in methanol (10 mL)-1N hydrochloric acid (5 mL) was stirred at 80°C for 12 hours. The reaction solution was poured into a mixture of diethyl ether and water, and an aqueous layer was then separated and concentrated. To the residue were added DBU (0.32 mL) and triethylamine (0.44 mL), which was dissolved in acetonitrile (10 mL). This solution was added to a suspension of 3-[(6-chloro-2-naphthyl)sulfonyl]propionic acid (0.32 g), WSC (0.30 g) and HOBt (0.24 g) in acetonitrile (10 mL) and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off.

The residue was purified with a silica gel column to obtain the title compound (0.27 g, 54%).

NMR (200 MHz, $CDCl_3$) δ: 1.65-1.84 (4H, m), 2.42 (3H, s), 2.86 (2H, t, J = 8.4), 3.18-3.26 (2H, m), 3.55 (2H, t, J = 8.4), 3.58-3.72 (2H, m), 3.83 (1H, m), 4.46 (2H, s), 6.87 (1H, s), 7.59 (1H, dd, J = 2.0, 9.0), 7.92-7.97 (4H, m), 8.47 (1H, s).

[0166]

Example 111

1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-[2-(1-methyl-1H-imidazol-5-yl)ethyl]piperidine

111a) Tert-butyl 4-[(Z)-2-(1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidinecarboxylate

Potassium tert-butoxide (0.21 g) was added to a solution of 4-formyl-1-trityl-1H-imidazole (Kelly, J. L. et al., J. Med. Chem., 20, 721 (1977)) (0.63 g) and (1-tert-butoxycarbonyl-4-piperidinyl)methyl(triphenyl)phosphonium iodide (WO 99/24421)(1.0 g) in THF (35 mL). After stirred for 12 hours, the reaction solution was poured into a mixture of ethyl acetate and an aqueous saturated ammonium chloride solution to separate an organic layer. The ethyl acetate solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (0.45 g, 51%).

NMR (200 MHz, $CDCl_3$) δ: 1.20-1.36 (2H, m), 1.45 (9H, s), 1.64-1.69 (2H, m), 2.67 (2H, t, J = 12.2), 3.05 (1H, m), 4.01 (2H, d, J = 12.8), 5.32 (1H, dd, J = 9.0, 11.6), 6.16 (1H, d, J = 11.6), 6.69 (1H, s), 7.10-7.20 (6H, m), 7.30-7.36 (9H, m), 7.43 (1H, s).

111b) Tert-butyl 4-[2-(1-trityl-1H-imidazol-4-yl)ethyl]-1-piperidinecarboxylate

A suspension of tert-butyl 4-[(Z)-2-(1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidinecarboxylate (0.43 g) obtained in Example 111a) and platinum oxide (0.08 g) in methanol (20 mL) was stirred at room temperature for 1 hour under hydrogen atmosphere. Insoluble substances were filtered off and the filtrate was concentrated to obtain the title compound (0.43 g, 99%).

NMR (200 MHz, $CDCl_3$) δ: 1.05-1.17 (2H, m), 1.45 (9H, s), 1.51-1.66 (5H, m), 2.52-2.68 (4H, m), 4.04 (2H, d, J = 13.5), 6.49 (1H, s), 7.11-7.18 (6H, s), 7.29-7.35 (10H, m).

111c) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(1-methyl-1H-imidazol-5-yl)ethyl]piperidine

Methyl iodide (1 mL) was added to a solution of tert-butyl 4-[2-(1-trityl-1H-imidazol-4-yl)ethyl]-1-piperidinecarboxylate (0.43 g) obtained in Example 111b) in acetonitrile (10 mL) and stirred for 12 hours. The reaction solution was concentrated and the residue was dissolved in methanol (10 mL) and 1N hydrochloric acid (5

mL). After stirred at 80°C for 3 hours, the reaction solution was poured into a mixture of diethyl ether and water and an aqueous layer was then separated and concentrated. To the residue were added DBU (0.25 mL), triethylamine (0.35 mL) and acetonitrile (10 mL). This solution was added to a suspension of (6-chloro-2-naphthyl)sulfonylpropionic acid (0.25 g), WSC (0.24 g) and HOBt (0.19 g) in acetonitrile (10 mL) and stirred for 12 hours. The reaction solution was concentrated under reduced pressure and the residue was dissolved in chloroform and an aqueous saturated sodium bicarbonate solution to separate a chloroform layer. The chloroform solution was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified with a silica gel column to obtain the title compound (0.29 g, 74%).

NMR (200 MHz, $CDCl_3$) δ: 1.05-1.28 (2H, m), 1.57-1.66 (3H, m), 1.73-1.86 (2H, m), 2.53-2.60 (2H, m), 2.85-3.07 (3H, m), 3.53-3.62 (2H, m), 3.56 (3H, s), 3.85 (1H, d, J = 13.8), 4.51 (1H, d, J = 13.8), 6.78 (1H, s), 7.40 (1H, s), 7.51 (1H, dd, J = 1.8, 8.8), 7.90-7.99 (4H, m), 8.50 (1H, s).

Elemental analysis for $C_{24}H_{28}N_3O_3SCl \cdot 0.5H_2O$

Calculated (%) C, 59.68; H, 6.05; N, 8.70.

Found (%) C, 59.58; H, 6.14; N, 8.43.

[0167]

Example 112

1-[3-[(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(2-methyl-1H-imidazol-4-yl)ethenyl]piperidine

112a) Tert-butyl 4-[(Z)-2-(2-methyl-1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidinecarboxylate

From 2-methyl-4-formyl-1-trityl-1H-imidazole (EP 451538 (1991)) (3.3 g) and (1-tert-butoxycarbonyl-4-piperidinyl)methyl(triphenyl)phosphonium iodide (5.0 g), the title compound (1.0 g, 22%) was obtained as colorless powder in a similar manner to Example 111a).

NMR (200 MHz, $CDCl_3$) δ: 1.20-1.31 (2H, m), 1.46 (3H, s), 1.56-1.63 (2H, m), 2.49-2.62 (3H, m), 3.97 (2H, d, J = 12.4), 5.28 (1H, dd, J = 8.8, 11.8), 6.18 (1H, d, J = 11.8), 6.61 (1H, s), 7.13-7.20 (6H, m), 7.30-7.37 (9H, m).

112b) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(2-methyl-1H-imidazol-4-yl)ethenyl]piperidine

From tert-butyl 4-[(Z)-2-(2-methyl-1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidinecarboxylate (0.39 g) obtained in Example 112a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.22 g), the title compound (0.25 g, 73%) was obtained as colorless powder in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 0.94-1.14 (2H, m), 1.19-1.26 (2H, m), 1.42 (1H, m), 1.64-1.76 (4H, m), 2.37 (3H, s), 2.47 (1H, m), 2.83-2.88 (2H, m), 2.96 (1H, m), 3.52-3.58 (2H, m),

3.79-3.84 (3H, m), 4.47 (1H, d, J = 12.8), 6.79 (1H, d, J = 1.2), 6.91 (1H, d, J = 1.2), 7.59 (1H, dd, J = 1.8, 8.7), 7.89-7.96 (4H, m), 8.47 (1H, s).

[0168]

Example 113

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(1,2-dimethyl-1H-imidazol-5-yl)ethenyl]piperidine

From tert-butyl 4-[(Z)-2-(2-methyl-1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidinecarboxylate (0.50 g) obtained in Example 112a), the title compound (0.16 g, 35%) was obtained as colorless powder in a similar manner to Example 111c).

NMR (200 MHz, $CDCl_3$) δ: 1.22-1.35 (2H, m), 1.65-1.82 (3H, m), 2.39 (3H, s), 2.59 (1H, t, J = 11.2), 2.82-2.92 (2H, m), 3.08 (1H, t, J = 11.2), 3.45 (3H, s), 3.52-3.62 (2H, m), 3.82 (1H, d, J = 11.2), 4.47 (1H, d, J= 11.8), 5.44 (1H, d, J = 9.6, 11.4), 6.05 (1H, d, J = 11.4), 6.88 (1H, s), 7.59 (1H, dd, J = 2.2, 11.2), 7.92-7.97 (4H, m), 8.48 (1H, s).

Elemantal analysis for $C_{24}H_{26}N_3O_3SCl \cdot H_2O$

Calculated (%) C, 58.83; H, 5.76; N, 8.58.

Found (%) C, 59.01; H, 5.46; N, 8.84.

[0169]

Example 114

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-(1,2-dimethyl-1H-imidazol-5-yl)methoxypiperidine

From tert-butyl 4-[(2-methyl-1-trityl-1H-imidazol-4-yl)methoxy-1-piperidinecarboxylate (0.50 g) obtained in Example 110a), the title compound (0.20 g, 44%) was obtained as colorless powder in a similar manner to Example 111c).

NMR (200 MHz, $CDCl_3$) δ: 1.42-1.61 (2H, m), 1.70-1.84 (2H, m), 2.37 (3H, s), 2.84-2.89 (2H, m), 3.18-3.28 (2H, m), 3.53 (3H, s), 3.51-3.67 (4H, m), 3.77-3.84 (1H, m), 4.46 (2H, s), 6.85 (1H, s), 7.58(1H, dd, J = 1.8, 8.7), 7.88-7.95 (4H, m), 8.46 (1H, s).

Elemental analysis for $C_{24}H_{28}N_3O_4SCl \cdot 0.25H_2O$

Calculated (%) C, 58.29; H, 5.81; N, 8.50.

Found (%) C, 58.29; H, 5.67; N, 8.56.

[0170]

Example 115

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(2-methyl-1H-imidazol-4-yl)ethyl]piperidine

A solution of 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(2-methyl-1H-imidazol-4-yl)ethenyl]piperidine (0.1 g) obtained in Example 112b) and platinum oxide (0.01 g) in THF (2 mL) was stirred for 6 hours under hydrogen atmosphere. Insoluble substances were filtered off and the filtrate was concentrated. The residue was purified with a silica gel column to obtain the title compound (0.06 g, 60%) as colorless powder.

NMR (300 MHz, $CDCl_3$) δ: 0.98-1.15 (2H, m), 1.53-1.60 (3H, m), 1.69-1.81 (2H, m), 2.39 (3H, s), 2.41-2.57 (3H, m), 2.82-2.88 (2H, m), 3.01 (1H, dt, J = 2.7, 13.2), 3.52-3.58 (2H, m), 3.78 (1H, d, J = 13.5), 4.44 (1H, d, J = 13.5), 6.60 (1H, s), 7.60 (1H, dd, J = 1.8, 8.7), 7.88-7.96 (4H, m), 8.47 (1H, s).

[0171]

Example 116

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(1,2-dimethyl-1H-imidazol-5-yl)ethyl]piperidine

From 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(1,2-dimethyl-1H-imidazol-5-yl)ethenyl]piperidine (0.5 g) obtained in Example 113), the title compound (0.3 g, 60%) was obtained as colorless powder in a similar manner to Example 115).

NMR (300 MHz, $CDCl_3$) δ: 1.02-1.19 (2H, m), 1.53-1.57 (3H, m), 1.76 (2H, dd, J = 15.9, 19.2), 2.36 (3H, s), 2.45-2.53 (3H, m), 2.84-2.90 (2H, m), 2.98 (1H, m), 3.41 (3H, s), 3.53-3.59 (2H, m), 3.84 (1H, d, J = 13.5), 4.48 (1H, d, J = 13.5), 6.14 (1H, s), 7.59 (1H, dd, J = 2.4, 9.3), 7.89-7.96 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{25}H_{30}N_3O_3SCl \cdot 0.5H_2O$

Calculated (%) C, 60.41; H, 6.29; N, 8.45.

Found (%) C, 60.40; H, 6.12; N, 8.24.

[0172]

Example 117

1-(2-{1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-piperidinyl}ethyl)-2-methyl-4,5,6,7-tetrahydro-1H-benzimidazole

117a) Tert-butyl 4-[2-(2-methyl-4,5,6,7-tetrahydro-1H-benzimidazol-1-yl)ethyl]-1-piperidinecarboxylate

From 2-methyl-4,5,6,7-tetrahydro-1H-benzimidazole (JP-A 49-31666) (0.93 g) and tert-butyl 4-(2-bromoethyl)-1-piperidinecarboxylate (2.0 g), the title compound (0.65 g, 27%) was obtained as a dark brown oil in a similar manner to Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.13-1.19 (2H, m), 1.45 (9H, s), 1.50-1.80 (9H, m), 2.33 (3H, s), 2.43-2.60 (4H, m), 2.60-2.78 (2H, m), 3.71 (2H, t, J = 7.2), 4.06 (2H, d, J = 14.2).

117b) 1-(2-{1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]}-4-piperidine}ethyl)-2-methyl-4,5,6,7-tetrahydro-1H-benzimidazole

From tert-butyl 4-[2-(2-methyl-4,5,6,7-tetrahydro-1H-benzimidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.57 g) obtained in Example 117a) and 3-(6-chloro-2-naphthyl-)sulfonylpropionic acid (0.56 g), the title compound (0.60 g, 61%) was obtained in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 10.7-1.19 (2H, m), 1.54-1.81 (10H, m), 2.34 (3H, s), 2.42-2.45 (2H, m), 2.52-2.56 (2H, m), 2.87 (2H, dt, J = 3.0, 7.2), 3.01 (1H, dt, J = 2.7, 13.5),

3.52-3.60 (2H, m), 3.72 (2H, t, J = 7.5), 3.84 (1H, d, J = 12.9), 4.50 (1H, d, J = 12.9), 7.59 (1H, dd, J = 2.4, 9.0), 7.89-7.96 (4H, m), 8.48 (1H, s).

[0173]

Example 118

1-(2-{1-{3-[(6-Chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl}ethyl)-4,5,6,7-tetrahydro-1H-benzimidazole

118a) Tert-butyl 4-[2-(4,5,6,7-tetrahydro-1H-benzimidazol-1-yl)ethyl]-1-piperidinecarboxylate

From 4,5,6,7-tetrahydro-1H-benzimidazole (WO 99/25710) (0.84 g) and tert-butyl 4-(2-bromoethyl)-1-piperidinecarboxylate (2.0 g), the title compound (1.37 g, 60%) was obtained as a dark brown oil in a similar manner to Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.13-1.19 (2H, m), 1.44 (9H, s), 1.50-1.80 (9H, m), 2.43-2.728 (6H, m), 3.80 (2H, t, J = 7.2), 4.06 (2H, d, J = 14.2), 7.29 (1H, s).

118b) 1-(2-{1-{3-[(6-chloro-2-naphthyl)sulfonyl]propanoyl}-4-piperidinyl}ethyl)-4,5,6,7-tetrahydro-1H-benzimidazole

From tert-butyl 4-[2-(4,5,6,7-tetrahydro-1H-benzimidazol-1-yl)ethyl]-1-piperidinecarboxylate (0.54 g) obtained in Example 118a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.56 g), the title compound (0.46 g, 47%) was obtained in a similar manner to Example 85b).

NMR (200 MHz, $CDCl_3$) δ: 1.07-1.16 (2H, m), 1.48 (1H, m), 1.59-1.82 (9H, m), 2.45-2.48 (2H, m), 2.58-2.61 (2H, m), 2.83-2.90 (2H, m), 2.99 (1H, m), 3.13-3.25 (3H, m), 3.52-3.58 (2H, m), 3.81 (3H, m), 4.49 (1H, d, J = 13.2), 7.30 (1H, s), 7.59 (1H, dd, J = 2.1, 9.0), 7.89-7.96 (4H, m), 8.47 (1H, s).

[0174]

Example 119

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(1,4-dimethyl-1H-imidazol-5-yl)ethyl]piperidine

119a) Tert-butyl 4-[(Z)-2-(5-methyl-1-trityl-1H-imidazol-4-yl)vinyl]-1-piperidine-1-carboxylate

From 5-methyl-1-trityl-1H-imidazole-4-carbaldehyde (Yuan, W. et al., J. Med. Chem., 36, 211 (1993)) (3.3 g) and (1-tert-butoxycarbonyl-4-piperidinyl)methyl(triphenyl)phosphonium iodide (5.0 g), the title compound (2.55 g, 56%) was obtained as colorless powder in a similar manner to Example 111a).

NMR (300 MHz, $CDCl_3$) δ: 1.22-1.39 (2H, m), 1.45 (3H, s), 1.46 (9H, s), 1.77-1.82 (2H, m), 2.80-2.88 (2H, m) 3.66 (1H, m), 4.08 (2H, br), 5.29 (1H, dd, J = 9.3, 11.7), 6.04 (1H, d, J = 11.7), 7.13-7.17 (6H, m), 7.27-7.36 (9H, m).

119b) Tert-butyl 4-[2-(1-trityl-5-methyl-1H-imidazol-4-yl)ethyl]-1-piperidinecarboxylate

From tert-butyl 4-[(Z)-2-(5-methyl-1-trityl-1H-

imidazol-4-yl)vinyl]-1-piperidinecarboxylate (1.5 g) obtained in Example 119a), the title compound (1.5 g, 99%) was obtained as colorless powder in a similar manner to Example 111b).

NMR (300 MHz, $CDCl_3$) δ: 1.22-1.39 (2H, m), 1.45 (3H, s), 1.46 (9H, s), 1.77-1.82 (2H, m), 2.80-2.88 (2H, m), 3.66 (1H, m), 4.08 (2H, br), 5.29 (1H, dd, J = 9.3, 11.7), 6.04 (1H, d, J = 11.7), 7.13-7.17 (6H, m), 7.27-7.36 (9H, m).

119c) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(1,4-dimethyl-1H-imidazol-5-yl)ethyl]piperidine

From tert-butyl 4-[2-(1-trityl-5-methyl-1H-imidazol-4-yl)ethyl]-1-piperidinecarboxylate (0.75 g) obtained in Example 119b), the title compound (0.22 g, 33%) was obtained as colorless powder in a similar manner to Example 111c).

NMR (300 MHz, $CDCl_3$) δ: 0.99-1.12 (2H, m), 1.37-1.52 (3H, m), 1.72-1.81(4H, m), 2.15 (3H, s), 2.45-2.56 (3H, m), 2.84-2.90 (2H, dt, J = 4.2, 6.9), 2.99 (1H, dt, J = 3.0, 12.3), 3.51 (3H, s), 3.55 (2H, dt, J = 4.2, 6.9), 3.83 (1H, d, J = 13.2), 7.28 (1H, s), 7.59 (1H, dd, J = 2.1, 9.0), 7.89-7.94 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{25}H_{30}N_3O_3SCl \cdot 0.75H_2O$

Calculated (%) C, 59.87; H, 6.33; N, 8.38.

Found (%) C, 60.01; H, 6.33; N, 8.38.

[0175]

Example 120

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(4-methyl-1H-imidazol-5-yl)ethyl]piperidine

From tert-butyl 4-[2-(1-trityl-5-methyl-1H-imidazol-4-yl)ethyl]-1-piperidinecarboxylate (0.66 g) obtained in Example 119b), the title compound (0.33 g, 57%) was obtained as colorless powder in a similar manner to Example 110b).

NMR (300 MHz, $CDCl_3$) δ: 0.99-1.16 (2H, m), 1.51-1.59 (3H, m), 1.70-1.81 (2H, m), 2.18 (3H, s), 2.44-2.55 (3H, m), 2.83-2.88 (2H, m), 2.98 (1H, dt, J = 2.4, 12.6), 3.53-3.59 (2H, m), 3.79 (1H, d, J = 13.5), 4.45 (1H, d, J = 13.5), 7.44 (1H, s), 7.59 (1H, dd, J = 1.8, 8.7), 7.88-7.96 (4H, m), 8.47 (1H, s).

Elemental analysis for $C_{24}H_{28}N_3O_3SCl \cdot 0.5H_2O$

Calculated (%) C, 59.68; H, 6.05; N, 8.70.

Found (%) C, 60.05; H, 6.24; N, 8.90.

[0176]

Example 121

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(1-methyl-1H-imidazol-2-yl)ethenyl]piperidine

121a) Tert-butyl 4-[(Z)-2-(1-methyl-1H-imidazol-2-yl)vinyl]-1-piperidinecarboxylate

From 1-methylimidazole-2-aldehyde (0.5 g) and (1-tert-butoxycarbonyl-4-piperidinyl)methyl(triphenyl)phosphonium

iodide (4.0 g), the title compound (0.72 g, 54%) was obtained as colorless powder in a similar manner to Example 111a).

NMR (200 MHz, $CDCl_3$) δ: 1.22-1.34 (3H, m), 1.46 (9H, s), 1.72-1.79 (2H, m), 2.86 (2H, t, J = 12.8), 3.61 (3H, s), 4.03-4.14 (2H, m), 5.63 (1H, dd, J = 9.6, 11.8), 6.10 (1H, d, J = 11.8), 6.82 (1H, d, J = 1.0), 7.07 (1H, d, J = 1.0).

121b) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl}-4-[(Z)-2-(1-methyl-1H-imidazol-2-yl)ethenyl]piperidine

From tert-butyl 4-[(Z)-2-(1-methyl-1H-imidazol-2-yl)vinyl]-1-piperidinecarboxylate (0.40 g) obtained in Example 121a) and 3-(6-chloro-2-naphthyl)sulfonylpropionic acid (0.45 g), the title compound (0.45 g, 71%) was obtained as colorless powder in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 1.14-1.34 (2H, m), 1.75-1.91 (3H, m), 2.67 (1H, dt, J = 3.0. 12.9), 2.83-2.90 (2H, m), 3.17 (1H, dt, J = 3.0, 12.9), 3.49-3.59 (2H, m), 3.62 (3H, s), 3.76 (1H, m), 4.24 (1H, d, J = 13.5), 5.55 (1H, dd, J = 9.3, 11.7), 6.11 (1H, d, J = 11.7), 6.83 (1H, d, J = 1.2), 7.06 (1H, d, J = 1.2), 7.59 (1H, dd, J = 1.8, 8.7), 7.89-7.96 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{24}H_{26}N_3O_3SCl\cdot\cdot0.25H_2O$

Calculated (%) C, 60.49; H, 5.61; N, 5.83.

Found (%) C, 60.67; H, 5.85; N, 8.59.

[0177]

Example 122

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[2-(1-methyl-1H-imidazol-2-yl)ethyl]piperidine

From 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[(Z)-2-(1-methyl-1H-imidazol-2-yl)ethenyl]piperidine (0.20 g) obtained in Example 121b), the title compound (0.19 g, 95%) was obtained as colorless powder in a similar manner to Example 115).

NMR (300 MHz, $CDCl_3$) δ: 1.02-1.16 (2H, m), 1.58-1.86 (5H, m), 2.52 (1H, dt, J = 2.7, 12.9), 2.67 (2H, t, J = 8.1), 2.83-2.88 (2H, m), 3.00 (1H, dt, J = 2.7, 12.9), 3.53-3.59 (2H, m), 3.57 (3H, s), 3.81 (1H, d, J = 13.2), 4.46 (1H, d, J = 13.2), 6.79 (1H, d, J = 1.5), 6.91 (1H, d, J = 1.5), 7.59 (1H, dd, J = 1.8, 8.7), 7.89-7.96 (4H, m), 8.48 (1H, s).

Elemental analysis for $C_{24}H_{28}N_3O_3SCl \cdot 0.3H_2O$

Calculated (%) C, 60.13; H, 6.01; N, 8.76.

Found (%) C, 60.21; H, 6.06; N, 8.46.

[0178]

Example 123

5-{1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-piperidinyl}imidazo[2,1-b][1,3]thiazole

123a) Tert-butyl 4-imidazo[2,1-b][1,3]thiazol-5-yl-1-piperidinecarboxylate

From tert-butyl 4-(1-bromo-2-oxoethyl)-1-piperidinecarboxylate (2.0 g) and 2-aminothiazole (0.77 g), the title compound (0.55 g, 23%) was obtained in a similar manner to Example 81a).

NMR (200 MHz, $CDCl_3$) δ: 1.48 (9H, s), 1.55-1.76 (2H, m), 1.96-2.05 (2H, m), 2.82-2.95 (3H,m), 4.19-4.26 (2H, m), 6.85 (1H, d, J = 4.4), 7.03 (1H, s), 7.33 (1H, d, J = 4.4).

123b) 5-{1-{3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-piperidinyl}imidazo[2,1-b][1,3]thiazole

From tert-butyl 4-imidazo[2,1-b][1,3]thiazol-5-yl-1-piperidinecarboxylate (0.55 g) obtained in Example 123a), the title compound (0.48 g, 55%) was obtained as colorless powder in a similar manner to Example 85b).

NMR (300 MHz, $CDCl_3$) δ: 1.52-1.77 (2H, m), 2.00-2.12 (2H, m), 2.75 (1H, t, J = 15.6), 2.90-3.05 (3H, m), 3.22 (1H, t, J = 15.6), 3.53-3.62 (2H, m), 3.97 (1H, d, J = 13.8), 4.59 (1H, d, J = 13.8), 6.86 (1H, d, J = 4.5), 7.01 (1H, s), 7.34 (1H, d, J = 4.5), 7.59 (1H, dd, J = 2.1, 9.0), 7.90-7.97 (4H, m), 8.49 (1H, s).

[0179]

Example 124

1-[3-(6-Chloro-2-naphthyl)sulfonylpropanoyl]-4-[4-(2-methyl-1H-imidazol-1-yl)butyl]piperidine

124a) Tert-butyl 4-[4-(2-methyl-1H-imidazol-1-yl)butyl]-1-piperidinecarboxylate

Tert-butyl 4-(4-bromobutyl)-1-piperidinecarboxylate (Egbertson, M. S. et al., J. Med. Chem., 37, 2537 (1994)) (2.0 g) and 2-methylimidazole (0.56 g), the title compound (0.94 g, 47%) was obtained as a light brown oil in a similar manner to Example 101a).

NMR (200 MHz, $CDCl_3$) δ: 1.03-1.35 (4H, m), 1.45 (9H, s), 1.59-1.82 (7H, m), 2.37 (3H, s), 2.66 (2H, t, J = 12.4), 3.81 (2H, t, J = 7.0), 4.06 (2H, m), 6.80 (1H, d, J = 1.4), 6.90 (1H, d, J = 1.4).

124b) 1-[3-(6-chloro-2-naphthyl)sulfonylpropanoyl]-4-[4-(2-methyl-1H-imidazol-1-yl)butyl]piperidine

From tert-butyl 4-[4-(2-methyl-1H-imidazol-1-yl)butyl]-1-piperidinecarboxylate (0.93 g) obtained in Example 124a), the title compound (0.1 g, 15%) was obtained as colorless powder in a similar manner to Example 85b).

NMR (200 MHz, $CDCl_3$) δ: 0.91-1.08 (2H, m), 1.22-1.43 (5H, m), 1.61-1.74 (4H, m), 2.37 (3H, s), 2.40-2.54 (1H, m), 2.81-3.02 (3H, m), 3.52-3.60 (2H, m), 3.78-3.85 (3H, m), 4.26 (1H, d, J = 13.2), 6.79 (1H, d, J = 1.4), 6.90 (1H, d, J = 1.4), 7.58 (1H, dd, J = 2.0, 8.8), 7.92-7.97 (4H, m), 8.47 (1H, s).

Elemental analysis for $C_{26}H_{32}N_3O_3SCl \cdot 0.5H_2O$

Calculated (%) C, 61.10; H, 6.51; N, 8.22.

Found (%) C, 61.21; N, 6.57; N, 7.95.

[180]

Formulation Example 1

A FXa inhibitor (e.g. deep venous thrombosis treating agent, cardiogenic cerebral infarction treating agent, etc.) containing a compound represented by the formula (I) of the present invention or a salt thereof as an active ingredient can be prepared, for example, by the following formulation.

1. Capsule

(1) Compound obtained in Example 24:	120 mg
(2) Lactose:	210 mg
(3) Microcrystalline cellulose:	27 mg
(4) Magnesium stearate:	3 mg
One capsule:	360 mg

(1), (2), (3) and 1/2 of (4) are mixed and then granulated. To this is added the remainder of (4), and the whole is encapsulated into a gelatin capsule.

2. Capsule

(1) Compound obtained in Example 68:	120 mg
(2) Lactose:	210 mg
(3) Microcrystalline cellulose:	27 mg
(4) Magnesium stearate:	3 mg
One capsule:	360 mg

(1), (2), (3) and 1/2 of (4) are mixed and then granulated. To this is added the remainder of (4), and the whole is encapsulated into a gelatin capsule.

3. Tablet

(1) Compound obtained in Example 68: 120 mg

(2) Lactose: 174 mg

(3) Cornstarch: 54 mg

(4) Microcrystalline cellulose: 10.5 mg

(5) Magnesium stearate: 1.5 mg

One tablet: 360 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. The remainders of (4) and (5) are added to this granule, which is compressed into a tablet.

4. Tablet

(1) Compound obtained in Example 72: 120 mg

(2) Lactose: 174 mg

(3) Cornstarch: 54 mg

(4) Microcrystalline cellulose: 10.5 mg

(5) Magnesium stearate: 1.5 mg

One tablet: 360 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then granulated. The remainders (4) and (5) are added to this granule, which is compressed into a tablet.

Formulation Example 2

After 50 mg of the compound obtained in Example 69 was dissolved in 50 ml of Japanese Pharmacopoeia distilled water for injection, Japanese Pharmacopoeia distilled water for injection is further added such that the whole volume

is 100 mL. This solution is filtered under sterilizing condition. One milliliter aliquot of this solution is filled into a vial for injection, lyophilized, and sealed.

[0181]

Experimental Example 1

(1) Human activated blood coagulation factor X (FXa) inhibitory activity

Experimental method: 225 μl of a 0.05 M Tris-HCl buffer (pH 8.3) containing 0.145 M sodium chloride and 2 mM calcium chloride, 5 μl of a sample (a test compound was dissolved in dimethyl sulfoxide) and 10 μl of human FXa (0.3 unit/ml) were added to a 96-well microplate and incubated at 37°C for about 10 minutes. Then, 10 μl of a substrate (3 mM, S-2765) was added to the plate and incubated at 37°C for 10 minutes. After stopping the reaction by adding 25 μl of a 50 % aqueous acetic acid, a change in absorbance at 405 nm was measured with a spectrophotometer, and the concentration (IC_{50}) at which 50 % of FXa activity was inhibited was calculated.

[0182]

(2) In vitro coagulation time measuring method

(2-1) Extrinsic coagulation time (PT) measuring method:

Extrinsic coagulation time was measured with an automatic blood coagulation time measuring apparatus (STA compact, DIAGNOSTICA STAGO) using a PT reagent (DIAGNOSTICA

STAGO). To 97 μl of human normal plasma (fresh human plasma FFP, Sekisui Chemical Co., Ltd.), 3 μl of a drug was added and preincubated at 37°C for 4 minutes. To 50 μl of the said plasma, 100 μl of a rabbit brain-derived tissue thromboplastin solution was added and then, a time required for coagulation was measured. A drug dissolved in dimethyl sulfoxide (DMSO) was used. The concentration of a drug required for 2-fold extension of a coagulation time was calculated based on a coagulation time when DMSO was added in place of the drug.

(2-2) Intrinsic coagulation time (APTT) measuring method:

Intrinsic coagulation time was measured with an automatical blood coagulation time measuring apparatus using STA-APTT-LT (DIAGNOSTICA STAGO). To 97 μl of human normal plasma, 3 μl of a drug was added. To 50 μl of the plasma, 50 μl of an activated partial thromboplatin solution was added and preincubated at 37°C for 4 minutes. Then, 50 μl of a 25 mmol/l $CaCl_2$ solution was added, and a time required for coagulation was measured. A drug dissolved in DMSO was used. The concentration of a drug required for 2-fold extension of a coagulation time was calculated as described in (2-1).

(2-3) Thrombin coagulation time (TT) measuring method:

Thrombin coagulation time was measured with an automatic coagulation measuring apparatus using a

fibrinogen reagent (DIAGNOSTICA STAGO). A fibrinogen reagent (containing thrombin) was dissolved in 5 mL of distilled water and then diluted 20-fold with a physiological saline supplemented with 0.5% bovine serum albumin. To 97 μl of human normal plasma (fresh human plasma FFP, Sekisui Chemical CO., Ltd.), 3 μl of a drug was added and preincubated at 37°C for 3 minutes. To 50 μl of the said plasma, 100 μl of a thrombin solution was added, and a time required for coagulation was measured. A drug dissolved in DMSO was used. The concentration of a drug required for 2-fold extension of a coagulation time was calculated as described in (2-1).

[0183]

(3) Ex vivo coagulation time measuring method (mouse)

(3-1) Intravenous administration:

A male ICR mouse (25-35 g, CLEA Japan Inc.) was used. To a mouse anesthetized with pentobarbital (50 mg/kg, i.p.), 5 ml/kg of a drug was administered once via a tail vein. After 5 minutes from administration, 0.8 ml of blood was taken from an abdominal aorta or heart using 1/10 volume of 3.8% sodium citrate (Citral, Yamanouchi Seiyaku) and then centrifuged at 3000rpm for 15 minutes to obtain plasma. To 50 μl of the said plasma, 100 μl of a rabbit brain-derived tissue thromboplastin solution was added, and a time required for coagulation was measured. A coagulation time

was measured with an automatic coagulation time measuring apparatus (STA compact) using a PT reagent (DIAGNOSTICA ATAGO). A drug dissolved in a mixed solution of dimethylacetamide and 1/10 N hydrochloric acid was used. A mixed solution of dimethylacetamide and 1/10 N hydrochloric acid was administered to a control group in place of the drug. The activity of the drug was expressed as the ratio (%) of a coagulation time of a drug-administered group to a coagulation time of a control group.

(3-2) Oral administration:

A male ICR mouse (25-35 g, Nippon Crea) was used. To a mouse which had been fasted for 12 hours or longer, 5 ml/kg of a drug was forced to be orally administered. After an hour from administration, blood was taken from an abdominal aorta under pentobarbital (50 mg/kg, i.p.) anesthesia. A drug suspended in 0.5% methylcellulose was used, and 0.5 % methylcellulose in place of a drug was administered to a control group. Others were as described in (3-1).

[0184]

(4) In vivo antithrombotic activity measuring method

(4-1) Rat arteriovenous shunt method:

The method was according to the method of Umetsu et al. (Thromb. Haemostas., 39, 74-73, (1978)). A male SD rat (200-350 g, Nippon Crea) was used. An extracorporeal

circulation path made of a polyethylene tube provided with a silk thread was placed between the left jugular and right jugular vein of a mouse anesthetized with pentobarbital (50 mg/kg, i.p.). In order to prevent blood coagulation, the tube was previously filled with a physiological saline containing heparin (50U/ml). Blood was circulated for 15 minutes, during which the wet weight of a thrombus attached to the silk thread was measured. A drug was administered orally or intravenously. In the case of oral administration, a drug (2 ml/kg) suspended in 0.5% methylcellulose was administered under fasting and 0.5 % methylcellulose was administered to a control group instead of a drug. In the case of intravenously administration, a drug (1 ml/kg) dissolved in a physiological saline was administered via a tail vein, and a physiological saline was administered to a control group instead of a drug. The activity of the drug was calculated as the ratio (%) of a thrombus wet weight of a drug-administered group to a thrombus wet weight of a control group.

(4-2) Rat abdominal vena cava partial ligation model

A male SD rat (200-400 g, Nippon Crea) was used. After the abdominal vena cava of a mouse anesthetized with pentobarbital (50 mg/kg, i.p.) was carefully peeled, two ligatures were put round a renal vein branched part of the abdominal vena cava and a place 1 cm downstream therefrom

respectively so that all branches between them were ligated. A balloon catheter (Fogarty 2F, Baxter) was inserted via the left femoral vein and the balloon was then dilated with a 200-300 ml air to damage three times between the two ligatures. The balloon catheter was taken out. The ligature put round the renal vein branched part was tied with a 26G needle and the needle was then taken out, thereby a partial ligation was made. After 30 minutes, the other ligature was tied, and a thrombus formed between the two ligatures was carefully isolated. The wet weight of the thrombus was measured using an analysis balance equipped with a windscreen (BP110S, Satorius). A drug was administered orally or intravenously as described in (4-1). The activity of the drug was calculated as described in (4-1).

(4-3) Rat.deep vein thrombosis (DVT) model

A male SD rat (200-350 g, Nippon Crea) was used. A polyethylene tube was inserted into the left femoral vein of a mouse anesthetized with pentobarbital (50 mg/kg, i.p.). A silk thread (length 5cm) connected to a guide wire was inserted into the polyethylene tube and the tube was filled with a physiological saline containing heparin (50U/ml) in order to prevent blood coagulation. After the polyethylene tube was inserted to reach the abdominal vena cava, the silk thread was allowed to be stood in the abdominal vena

cava using the guide wire. After 30 minutes, heparin (200U/kg) was intravenously administered via a tail vein. After exsanguinations by cutting of an upper arm artery, the abdominal part was opened to take out the silk thread and the wet weight of thrombus attached thereto (including weight of silk thread) was measured. A drug was administered orally or intravenously as described in (4-1). The wet weight of only thrombus was calculated using the equation: (wet weight of thrombus attached to silk thread) - (wet weight measured of silk thread immersed in a venous blood sample collected using heparin). The activity of the drug was calculated as described in (4-1).

[0185]

Experimental results

Table 1 shows IC_{50} values obtained in Experimental Example 1 (1). From this, it is clear that the compound of the present invention shows excellent FXa inhibitory activity.

Table 1

Example No.	IC_{50}(nM)	Example No.	IC_{50}(nM)
24	31	38	11
39	11	42	7.1
68	5.6	72	7.2
102	43	109	45

[0186]

Effect of the Invention

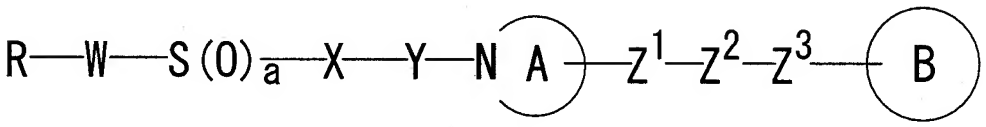
Compound (I) of the present invention or a salt thereof has excellent FXa inhibitory activity with less side effects of bleeding, is useful as an anticoagulant which can be orally absorbed, and is advantageously used for preventing or treating various diseases based on thrombus or infarction.

Document Name: Abstract

Problem: To provide an imidazole derivative useful as a thrombosis treating agent.

Solution: A compound represented by the formula (I):

[Chemical formula 1]



(I)

wherein R represents an optionally substituted cyclic hydrocarbon group or an optionally substituted heterocyclic group, W represents a bond or an optionally substituted divalent linear hydrocarbon group, X represents an optionally substituted divalent hydrocarbon group, Y represents -CO-, -S(O)-, $-S(O)_2-$ or a bond, ring A represents an optionally substituted pyrrolidine ring, an optionally substituted piperidine ring or an optionally substituted perhydroazepine ring, Z^1 and Z^3 independently represent a bond or an optionally substituted divalent linear hydrocarbon group, Z^2 represents $-N(R^1)-$, -O-, -S(O)-, $-S(O)_2-$, -CO-, $-CH(R^1)-$ or a bond (wherein R^1 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, an optionally esterified carboxyl group, or an optionally substituted carbamoyl group), ring B represents an optionally substituted imidazole ring, wherein a substituent which the optionally substituted imidazole ring

represented by ring B may have may be taken together with R^1 to form an optionally substituted ring, and a represents 0, 1 or 2, or a salt thereof.

Selected Figure: none